EXHIBIT B

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED, Plaintiff, vs. VYSIS, INC., Defendant.	)	No. 99CV 2668H (AJB)

DEPOSITION OF KARY B. MULLIS, Ph.D.

Newport-Beach, California

Friday, November 2, 2001

Reported by:
LINDA L. SILVER
CSR No. 9915
JOB No. 141508

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE, INCORPORATED,	)	
	)	
Plaintiff,	)	
	)	
vs.	)	No. 99CV 2668H (AJB)
	)	
VYSIS, INC.,	)	
	)	
Defendant.	)	
	)	

Deposition of KARY B. MULLIS, Ph.D., taken on behalf of Defendant, at 1107 Jamboree Road, The Palm Room, Newport Beach, California, beginning at 9:50 a.m. and ending at 2:39 p.m. on Friday, November 2, 2001, before LINDA L. SILVER, Certified Shorthand Reporter No. 9915.

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EXHIBITS FOR REFERENCE

Newport Beach, California, Friday, November 2, 2001

9:50 a.m. - 2:39 p.m.

THE VIDEOGRAPHER: Good morning. Here begins videotape number one in the deposition of Kary B. Mullis in the matter of Gen-Probe, Incorporated versus Vysis, Incorporated in the U.S. District Court Southern District of California, the case number of which is 99CV-2668H (AJB).

Today's date is November 2nd, 2001. The time is 9:50 a.m. This deposition is being taken at 1107 Jamboree Road, Newport Beach, California and was made at the request of L. Scott Burwell of the Law Offices of Finnegan, Henderson, Farabow, Garrett & Dunner.

The videographer is Mike Henry with Esquire Deposition Services of Washington D.C.

Would counsel and all present please identify yourselves and state whom you represent.

MR. LIPSEY: Charles Lipsey with Finnegan, Henderson, Farabow, Garrett & Dunner representing the defendant Vysis, Incorporated, and joined by my colleague Scott Burwell.

MR. SWINTON: Steve Swinton on behalf of Gen-Probe.

THE VIDEOGRAPHER: Thank you.

Would the court reporter please administer the oath to the witness.

KARY B. MULLIS, Ph.D.,

having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. LIPSEY:

Q Good morning.

A Good morning.

Q Would you state your full name and residential address for the record, please.

A Kary B. Mullis, and 919 Bayside Drive, Apartment O-4, Newport Beach, California, 92660.

9:52

Q By whom are you currently employed?

A By a number of different people. I do a lot of consulting, and also I am a traveling lecturer, so there are a whole bunch of different people that end up paying me at any one time.

9:52

Q You're basically self-employed; is that right?

A Yes.

Q I gather you perform consulting services for a number of companies; is that right?

A Yes. Mainly what I do now is give lectures,

which is a lot more fun.

Q You're appearing here today as an expert witness on behalf of Gen-Probe; is that right?

A Yes.

Q When were you retained as an expert witness for Gen-Probe?

A I think it was about a year ago, year and a half ago, something like that. I actually can look that up if you need to know.

Q No, general time frame is close enough.

How did you come to be retained as an expert for Gen-Probe?

A I -- my recollection is that Bill Bowen called me on the telephone, and I'm not sure how he got my phone number, but it's not hard to find.

Q Did you know Mr. Bowen?

A I didn't know him prior to that.

Q Had you had any connection with Gen-Probe prior to that?

A I can't recall ever having any specific connection with them. I certainly knew people in San Diego that worked there whose names I could probably dig up if I needed to, but I've never -- I never worked for them, and I don't think I ever did any kind of legal consulting or biochemical consulting for them.

Q Did you know Dan Kacian?

A The name doesn't sound real familiar. I don't think I knew him.

Q Had you had any connections with Chiron prior to the time you were retained as an expert in this case?

A Let's see, I think I must have consulted for them at least on one occasion, and I was quite familiar with Ed Penhope, the president of Chiron and one of the founders, and Mickey Urdea. They were across the street from me. When I worked at Cetus, Chiron was formed, and their offices and laboratories were right across the street from us. So I had a good bit of interaction with them for a while while I was still working at Cetus.

Q When is the last time you -- well, are you on retainer or any such arrangement with Chiron?

A With Chiron, no.

Q When was the last time you performed any consulting services for Chiron?

A It would have been probably in the like 1988, somewhere around there. And I'm not really certain. I know I went there, gave lectures. Whether they paid me or not, I can't remember right now. They would have to now. But I think there was like a period when I maybe consulted with Mickey Urdea there a couple of times.

Q Have you had any consulting arrangements with

a Japanese company, Chugai Pharmaceuticals?

A Let's see, the question is whether I've been a consultant for them?

Q Yes.

A No, I've not consulted for them, but a company here that I -- here in Newport Beach or actually here in Irvine county called Burstein Labs had some corporate interaction with them. Well, it was being explored and I think Chugai backed out of it, but I met with some Chugai people in the last year. Not with anything to do with this case. It was something entirely different.

Q Okay. Have you had any consulting arrangements with the German company Bayer or any of its associated companies?

A I'm not certain about its associated companies, but not directly -- I mean, I've never been hired by somebody that called themselves Bayer. They might have a lot of different little outfits. I've consulted for a lot of little companies, usually just one or two times, so it's a whole long list of companies that I've consulted for.

Q Do you have an ownership or equity position in any company now?

A I have a lot of stock options for this company Burstein Technologies that I mentioned that had the

interaction with Chugai, and -- you mean like sometimes trying to make money and losing it, that kind of stock? I've certainly bought and sold, usually buying high and selling low. But right now I probably have a number of shares in, you know, a whole slew of little biotech companies, but Gen-Probe is not one of them. And I don't know if I've ever owned any of their stock or even if it's -- I assume they're a publicly held company.

Q What is the business of the company you mentioned, Burstein?

A Burstein, they're developing a diagnostic system based on optical disk drives, and it's like a general diagnostic system. The thing that I -- when I was working there actively, I -- in my lab we were developing a way to look at bacteria in urine samples.

We were also developing amplification techniques, more basically PCR-type techniques that could be done on a disk inside of a disk drive.

Q Did that technology combine a target capture step with amplification?

A We never really -- we never got it to the point where we would have had to -- never got to the point we were working with real samples where we might have had to pull some DNA out of it. We were working with, like, laboratory samples that already had been cleaned. We

were basically just working with the process of how do you do an amplification on a spinning optical disk.

Q Okay. I saw from your CV that you had had some experience testifying in what appeared to be criminal cases. Have you ever testified in a civil case before?

A Yes.

Q Any of those patent cases?

A There seems like it's an ongoing patent case with regard to PCR just about everywhere all the time, and with, let's see -- at like the company like Hoffman La Roche, I've testified from them. Also for Applied Biosystems, they have PCR kind of issues occasionally. Perkin-Elmer.

Q In those cases, are you testifying as a fact witness about your work with PCR, or were you testifying as an expert as you are in this case?

A Generally --

MR. SWINTON: I'm sorry, Dr. Mullis, from time to time I may need to interrupt only to assert an objection. I'm not intending to stop you from giving the answer, but just so the court reporter doesn't have to fight over us.

The objection I was going to assert is that it may call for you to speculate and calls for a legal conclusion about the actual nature of your testimony.

That's my objection for the record only. Please proceed to answer.

THE WITNESS: Okay. I as far as I know, not being a lawyer, I just believe what they tell me, I have done both. I mean, I've been -- I have some idea of what the difference is, but I mean, you know, PCR court cases have drug out for years and years, and I get involved in them in different ways, but I think at least two of them have been as a fact witness.

BY MR. LIPSEY:

Q Okay, but you believe in some of them you've been an expert also?

A Yes, and I think the bulk of the time that I've been in courtroom situations, it's been as an expert. My idea of what that is is -- may be probably not what it is, but I think --

Q I'd love to take up your time asking for a list of those instances where you've testified.

Mr. Swinton, perhaps could you agree to provide us with a list of the instances where Dr. Mullis has testified and that way we don't have to take up his time?

MR. SWINTON: If you cut short the 7 hours, I'll be happy to do that. I'm not sure I want to accommodate just to extend this out for more time but to

the extent we can, we'll try.

THE WITNESS: I think maybe my CV that was sent to you doesn't contain all of that, but I thought there was one section of it that talked about testifying in various -- my wife, I think sent that, and there is different versions of it, but --

MR. LIPSEY: Well, why don't we mark for identification as Defendant's Deposition Exhibit 197 a copy of the CV of Dr. Mullis that we have, and if it's not the right one, then we'll find out soon enough.

10:01

(Defendant's Exhibit 197 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q I guess just for the record, is Defendant's Exhibit 197 a copy of your CV?

A Yes.

Q And to the extent it contains information, is it your brief that it's true and accurate?

10:02

A Yes.

Q Okay. Now, can you tell from examining it whether it lists the instances in which you have previously testified?

A You know, I think that what has been done here is the companies that I've maybe -- you know, like it mentions like Applied Biosystems here, Orrick,

Herrington and Sutcliffe:PE Applied Biosystems. This is in the part that is called "Private Consultant," and I think I've put those things that were noncriminal things in with those companies that I consulted for.

That's what I've -- it's -- it doesn't, for instance, say, McCutchen, Doyle, Enersen & Brown, San Francisco, it doesn't say that was a legal case, but that's what that was. There is a number of those like Orrick, Herrington, Sutcliffe, obviously that was one of those, Perkin Elmer, Foster City. I've had --

Q Is it your belief you have a list of the actual cases in which you've testified someplace?

A I have had files and stuff on that, and I could prepare such a list if you wanted to see that. I guess I didn't make that specific here.

MR. LIPSEY: Okay. Counsel, rather than take Dr. Mullis's time to do that, I would renew my request that you provide us with a list of the cases in which Dr. Mullis has previously testified.

MR. SWINTON: Beyond that that is required in the disclosure? I just want to make sure I know what you're asking for.

MR. LIPSEY: I'd like the complete list.

MR. SWINTON: If we can reasonably do it, I'll endeavor to do that.

MR. LIPSEY: I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 198 a copy of a document entitled "Expert Report of Dr. Kary B. Mullis Pursuant to Fed.R.Civ.P.26."

10:04 For efficiency, let's go ahead and mark as Defendant's Deposition Exhibit 199 a copy of a document entitled "Declaration of Dr. Kary B. Mullis in Support of Gen-Probe Incorporated's Motion for Partial Summary Judgment of Noninfringement Under the Doctrine of Equivalents."

10:04 (Defendant's Exhibits 198 - 199 were marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Just for the record, Dr. Mullis, is Defendant's Deposition Exhibit 198 a copy of the expert report you have submitted in connection with this case?

A It appears to be.

Q Now, I note from the last page of the report

10:05 itself, page 20, that you signed it on September 26, 2001; is that right?

A Yes.

Q And I note from page 16 of Defendant's Deposition Exhibit 199, which is a declaration of yours, that you signed it on September 26, 2001 also; is that

10:05 right?

A I'll take your word for it unless you want -- yes, September 26, that's right.

Q Without trying to belabor the point, is it your understanding that the substance of your report and the substance of your declaration both executed on September 26, 2001 is the same?

A Is the substance of the two the same?

10:06 Q Right.

MR. SWINTON: Objection; the documents speak for themselves. Notwithstanding, the documents being the best evidence, go ahead and answer.

THE WITNESS: I don't think there is any differences of like factual or speculative kind of stuff in them. I think they cover the same kind of material.

BY MR. LIPSEY:

Q And is it your recollection that they express basically the same opinions?

MR. SWINTON: Same objection.

THE WITNESS: It is -- you know, without your being a little -- there is a lot of opinions in there,

10:06 and I think that my opinions on matters in this case haven't changed between the one and the other. They certainly should reflect the same general ideas.

BY MR. LIPSEY:

Q I guess I was hoping to short circuit the whole

process, because it looks to an outsider as if the two documents were prepared together, and one was in the form of a report and one was in the form of an affidavit.

Is it your recollection that is the way it was done?

A Yes, yes.

Q Now, referring to your report, Defendant's Exhibit 198, can you describe the process by which that report was prepared.

A There were a lot of conversations with Bill Bowen. There were some documents -- he -- I sent him some written material. He sent me some. We went -- you know, he incorporated the stuff I had sent him into a sort of a format that looked more like a lawyer had written it, and we just -- you know, we worked on it together that way.

And in every case, it would come back to me for like the final approval of how he described -- and in a lot of cases he just used my words verbatim, and in some places he would, like describe things that we talked about in his own way, but in a way that I agreed with.

Q Do you have the draft materials that were used in the process you just described?

A Yeah, I think I have those -- they're like -- I

10:08 think I do. Do you want to see them?

Q Sure.

A I think you've probably got them already in the things that I sent to Bill.

Q Okay. I see now that you have a folder of things that you brought with you. Is all of that ultimately intended for us?

10:09 A If you want to see it. I didn't bring everything I've ever read in my life, which is what you asked me to do, and I thought that was rather rude, the way that you stated the things that I should bring was absolutely absurd or somebody did. But these are the things that I think of as being pertinent to this particular case in terms of things that I've had some input in. I figure you've got your own copies of the patents and all of the literature and stuff.

MR. LIPSEY: Okay. Well, with your permission, 10:09 Counsel, if the witness can share that with us, we'll try to look at it at a break and try to minimize the amount of time we take.

Thank you.

Q Okay. I would like to find out what materials you considered in formulating the opinions that you've expressed in your expert report, Exhibit 198.

10:10 A Well, certainly I was furnished a copy of the

patent, the `338 patent. I was -- and I think I also looked at fairly lengthy reports from, I think this man's name is Persing, his opinions. Specific things, I mean, it's hard to say where, you know, something starts being specific.

10:10

I've had a long history in the area of amplification, so occasionally I look at articles and things that I don't really copy and say I've now looked at this article, but, I mean, I have a general awareness of the literature for the past 20 years in the area of amplification, and I certainly refer to that, if not specifically article by article, I mean, that's my background.

Q Can you recall any articles you specifically consulted?

10:11

A Not -- I can't recall any specific ones.

Q Were there any other materials --

A I mean, I've looked at my own patents in this area. I remember pulling those out and just looking at what was going on back in -- trying to remember what was going on in 1985, that kind of thing, and one way to do that is to go back and look at things that I'd written during that period. So I would have to say that.

10:11

Q That's the sort of thing that I'm interested in. So you looked at your own patents?

A Um-hum.

Q Did you look at any of your own articles from that time?

A Yes.

Q Can you identify to the best extent that you can what those were?

A I think I could probably do it better if I was looking at my CV here. There is a list of my patents in the CV, and I didn't look at all of these, but any -- I certainly --

10:12

Q Stop right there. Do you remember which patents you looked at?

A The `202, the one that we talked about, the PCR patent called the `202.

Q Okay. Any others?

A And I think the `198, I believe those are the numbers on it. No, I'm sorry, it's the `195. The `202 and `195. U.S. 4,683,202 and U.S. 4,683,195. I remember looking at those just to see in my memory what was going on there.

10:12

Q Before we leave the patents, were there any of the others that are listed there in your CV, Defendant's Exhibit 197, that you remember looking at in connection with preparing your report?

A I don't remember looking at any other ones

specifically, but I may have. I don't remember not -- I mean, I have a box full of them, and I probably looked at them, if they had any relevance, and some of them did.

Q But like what?

A Well, I was trying to figure out why -- why this particular -- this `388 (sic) patent never got applied for or issued, and I was trying to understand what sort of the basis of the -- what was the original basis of that patent and how did it get to be the way it was sort of, and I think part of that was looking back at what things had already been patented in that area at the time of the `388's being issued.

Q Did you find in your review that the subject matter of the `338 patent had already been patented by somebody else?

MR. SWINTON: Calls for a legal conclusion, beyond the scope of his opinions.

THE WITNESS: I would go with that. I couldn't understand why somebody would have applied for it, I guess. I mean, it's the same thing. I didn't see any kind of real original material in the `388 to tell you the truth.

BY MR. LIPSEY:

Q I guess my specific question is, in your

review, did you find a patent that had been issued to somebody else on the subject matter of the '338 patent?

10:14 MR. SWINTON: Same objection; legal conclusion, beyond the scope of his opinions.

THE WITNESS: There were a lot of commonly used procedures that I was -- I was familiar with and where I could have probably found at least literature referring to. The things like, you know, mRNA and cloning stuff like that that I think bears on the patentability of the material in the `388 that I could have found places in

10:15 literature that -- because my knowledge of that stuff is sort of general. I didn't have to go to specific spots and say, "This particular article or this claim of this patent is talking about something that seems to be patented in the `388." I didn't go to that level of detail.

BY MR. LIPSEY:

Q Okay. We were getting back to the materials

10:15 that you had reviewed in preparing your opinion, and I think you said you had looked at some articles also, and you were about to look in your CV, Defendant's Exhibit 197, to see if we could figure out which ones those were.

A Things like -- well, there are quite a few of them in here, and I don't have any specific ones marked

that I specifically referred to, but, you know, articles like Mullis, Faloona, Scharf, Saiki, Horn and Erlich, Quantitative Biology 51. It was like in 1986. It was like an early description of PCR, which I think I just looked through that to see --

Again, you know, with the idea in mind of saying what was happening in 1986 that sort of formed the context for this patent having been issued. I mean, I was kind of puzzled why the thing was issued, and I was looking back saying how is it that some patent examiner would think these things weren't already being done in someway or other? It was not my business to do that because I'm not a patent lawyer, but I was curious.

Q So you've identified the Mullis, Faloona and others article in --

A Cold Spring Harbor Symposium article in Quantitative Biology 51. That was like a real early PCR publication, and there are several others around in that same time period that I'm sure I looked at.

Q Do you recall specifically which those were?

A Well, if -- they're like -- there is one in Nature 324 : 6093 (1986).

Q That's the next reference on that page of your CV?

A Yes.

Q Okay. Any others?

A I think I probably looked at this Kwok paper. It was the Journal of Virology 61 : 1690 (1987). I think I looked at that. That was a paper where the -- there was some need for some prepurification there of samples that had very low levels of HIV.

Q Any others?

A I wouldn't specifically point to any others. Like I said, I have boxes of papers, you know, and when I'm working on something like this, I might leaf through a whole lot of them to find specific things, but I don't make a record necessarily of which ones I've looked at.

Q So you've identified for me the ones that you remember looking at; is that true?

A Yes.

Q While we're on this page of your CV, which of these articles is the first publication describing PCR?

A That's the Science 230 (1985), the paper that starts off with Saiki's name.

Q Do you recall when in 1985 that was published?

A Right around Christmas.

Q Okay. Were there any other materials that you reviewed in formulating the opinions expressed in your expert report in this case?

A I can't remember any specific ones.

Q Did you have the expert reports of any witnesses other than Dr. Persing?

A You know, I think there were. I think there was a packet that had some -- yeah, there was some other 10:19 expert, I think, working for Gen-Probe, and I can't recall that person's name, but as I remember at some point seeing like his response to Persing. And I should be able to recall his name, but I can't.

Q Just to run through some of them, Harpold, is that the name? Or Falkinham?

10:20 A Falkinham sounds right.

Q Falkinham. Okay. But you don't recall having a report by Dr. Harpold; is that right?

A I don't specifically recall that one.

Q Any other expert reports -- and I would include in there draft expert reports so that there is no ambiguity -- from any of the other witnesses that you had and considered in preparing your opinion?

A I can't recall any others specifically.

Q Were there any other materials that you 10:20 reviewed or considered in connection with preparing your report, other than those you've identified to me?

A I can't remember any others.

Q How long did this process of preparing your

report take?

A I think it was -- probably went on for a matter of months. You know, when we first started sending back a -- I don't remember when I first sent Bill like two or three pages of my comments about the thing, when that first happened, but I would sort of consider that the beginning, and I might be able to find it. If you give me back all of those papers, I can look at the dates of some times when I sent him a bill. I might be able to figure out from that when the first time --

Q Sure, I'll hand back the collection of papers.

A It's somewhere in here. I thought it was in here.

No, you know, I was thinking this might contain that information, but this starts September the 17th, 2001, and I'm certain this was going on long before that. This is the last sort of invoice that my wife prepared for Bill Bowen, and I thought it covered the whole time, but it didn't. So I don't know exactly when that first stuff started going back and forth. It was a long process, I remember that. Nobody seemed to be in a rush either.

Q Thank you.

How much time in the aggregate have you spent on this case?

A I would say somewhere around maybe three to five days, that's eight hours spread out over a long period of time. I'm guessing there, but I think that's about right. I've been traveling a lot and coming back to this, and, you know, it has just happened periodically, so I'm not really sure.

Q I think I saw in your expert report you're charging a fee of $5,000 a day; is that correct?

A For doing a deposition. Maybe it's $5,000 a day for even working on it. I'm not certain. I thought it was 4, but maybe it's 5.

Q Okay. So --

A I have a very efficient wife/manager who takes care of those things.

Q It's $4- or $5,000 a day for work other than testifying, and $5,000 a day to testify; is that right?

A Right. It may be that she's raised me up to 5 for working.

Q Do you know what criteria she uses for determining what your daily rate is?

A Well, whatever the traffic will bear. I'm traveling around the world now giving lectures, and that's where I start, just to give a lecture, and this takes more time actually, and it's not nearly as much fun. I'm not trying to get a lot of this particular

kind of work by lowering the price.

Q So you're not the low cost provider of expert opinion; is that right?

A That's right. I'm not interested in bulk testimony.

Q Do you prorate that rate, or is that what you charge for any day on which you work on the case?

A No, that's -- that's for, like I said, an eight-hour day.

Q What, if anything, have you done to prepare for this deposition today?

A I read over the materials that I had provided Bill already and the things that had been sort of finalized like these documents. I last night read over some -- let's see, it was like a response. There was a nice little thing which is probably in that folder I gave you where the positions of Vysis and Gen-Probe are sort of matched against each other, and it's kind of an outline. I looked fairly carefully at that.

Q Anything else?

A I guess, I don't think anything specifically that I recall. This would have been like yesterday.

Q Okay. How much time did you spend yesterday?

A I think I spent about four hours.

Q Okay. Did you spend any time before yesterday

getting ready for the deposition?

A I think the day before yesterday I spent about an hour.

Q Any time before that?

A And I think previous to that it goes back into September or something.

Q Did you have any meetings or telephone conversations regarding preparation for this deposition?

A Very brief with Steve, probably two days ago. Not really terribly substantive. Most of the substantive comes by e-mail and, you know, documents.

Q What had you gotten by way of e-mail?

A Well, that's, like yesterday, that little thing I was talking about that is in there, it's an outline. The one thing that I kind of recall is sort of a structured looking page with little boxes saying here is what Vysis is saying and here is what Gen-Probe is saying on various issues.

Q That's something that you got from Gen-Probe's lawyers?

A Yes.

Q Anything else that came by e-mail?

A There were a number of documents. There was like a -- I can't remember what the names of them are. I think they're in that stack there.

Q Okay. By the stack, you mean the materials that you brought with you this morning?

A The stuff I gave you in that folder, I believe, is all of the things.

Q Any other -- how long did your meeting with Mr. Swinton last?

A You mean the telephone conversation?

Q Oh, I'm sorry, yes, the telephone conversation.

A I talked to him also this morning before we came over here, but the telephone conversation was very brief.

Q Okay. Was anybody else on the phone?

A No.

Q How long did you meet this morning with Mr. Swinton?

A I think he got there a little after 8:00, so we were probably sitting there for about an hour before we came over here.

Q Did you review any documents this morning in preparing to testify?

A I was looking at some of this -- I had them spread out on my table from last night, and they were there. We didn't study any one of them in particular, but we just talked mostly.

Q But the ones that you had before you were the ones in the folder that you brought with you this morning?

A Yes.

Q Were there any others?

10:28 A No, I brought everything that was there on the table.

Q Now, are there -- what issues were you asked to consider as an expert in connection with this case?

A I think in general -- most of the issues that I 10:29 have been considering, I assume it's because I was asked, have to do with what is sort of what do you mean by specific and non-specific amplifications and how can you compare those, you know, in reasonable ways. I think that was -- that's the crux of the whole thing, well, what is the --

Although, I can remember when reading that original patent, I thought of a lot of different things in there like prepurification of samples by various 10:29 methods, what that does and what it doesn't do. So the issue of specificity, I think has been the uppermost.

Q Okay. I gather you understand you were asked to express an opinion on the issue of infringement in this case; is that right?

A Well, putting it that -- I certainly did

express opinions, I think from time to time. But I don't remember being -- was I supposed to -- I think that's kind of a legal thing, isn't it, to say whether there is infringement or not? I don't usually get asked that kind of thing, but I certainly have mentioned that. I mean, it's not beyond me to see what is obviously an infringement and what is not, but the details I might get a little confused about.

Q Let me try using a different word. Is it your understanding you were asked to express an opinion as to what was and was not covered by the claims of the `338 patent?

A Yes.

Q Were you asked to express opinions on any other issues?

A Any other issues besides what was covered by the patent claims of the `338?

Q Right.

A For example, give me -- what would you consider another issue?

Q Were you asked to express an opinion as to whether the subject matter claimed in the `338 patent was either novel or non-obvious?

A I think I probably was -- there were a lot of discussions about that. Whether I was specifically

asked that, I'm not sure, but I think I made some remarks in written form that you've got in that purple folder relative to that.

Q Okay. But none of those remarks found their way into your expert report, which is Exhibit 198, correct?

10:31

A Well, I'd have to look through it to see whether they did, but I think all -- I mean, that was the purpose of the whole thing, right?

Q You tell me.

A Well, it seems like that was what most of this was about. You want me to look through this Exhibit 199 and see if I can find anything relevant to whether there was any original content in the `388 or something like that? Is that what you're asking?

Q I'm asking whether you expressed in your report an opinion as to the novelty or non-obviousness of the subject matter claimed in the `338 patent, and if you did, I'd like to know where it is.

10:32

A Okay, well, let's see, of the novelty of the `388?

MR. SWINTON: Objection; calls for a legal conclusion.

BY MR. LIPSEY:

Q Well, let me try to cut through it a little

bit.

You've got a bunch of patents yourself, right, Dr. Mullis?

A Yes.

Q And those patents have been involved in litigation for years, right?

A Yes.

Q And you've been involved, at least peripherally, in that litigation for years, correct?

A Right.

Q And you understood that in patent litigation that one of the issues involved is whether or not the party charged with infringement is infringing the patent, right?

A Yes.

Q And you understood that an issue that can arise in patent litigation goes to validity of the patent, right?

A Actually, I didn't know that until this morning. I wasn't certain. I thought those were two separate issues. I thought the one idea was whether somebody is infringing a patent, assuming that the patent is, in fact, valid, and that would be a separate legal issue, I thought, to challenge the validity of the patent. I was told this morning, no, that those can

happen at the same time.

Q But was it your understanding that in your report you were expressing opinions on whether or not the claims were being infringed, assuming they were valid, and not expressing an opinion as to whether or not the claims were valid or invalid?

A I really didn't -- I don't think I defined that for myself in any particular way. You could just read what I have to say, and I can answer questions about it that have to do with what I said. I didn't decide, "This is my response to this issue, and this is my response to this issue" when I was writing these things. I was just sort of looking at the whole thing, you know, from my point of view.

I mean, did you read the things that I wrote and do you have something specific in mind because I'll look at it and read it and see if that means something to me. It's not meaning much to me what you're saying.

Q I read your report and it looked to me to relate to the issue of infringement, and I have a whole bag of things to ask you if it relates to something other than infringement, and so the question is should I pull it out of my bag and ask you about it or should we talk about infringement?

MR. SWINTON: My objection is he was not --

it's clear in the report, the document speaks for itself, Dr. Mullis was asked to opine about the issue of infringement. I think you're trying to confuse things.

MR. LIPSEY: That's fine.

MR. SWINTON: Dr. Mullis --

MR. LIPSEY: That's fine, Counsel. I'm happy to take it from you. I just don't want to hear about it later that there was something else in there.

MR. SWINTON: Fine.

BY MR. LIPSEY:

Q Okay. Now, in preparing your report, did you review the prosecution history of the `338 patent?

A I think in -- I mean, the prosecution history would include those documents like, say, Persing's declarations or whatever, Falkinham's comments. Is that what you mean by the prosecution?

Q Let's go back and lay a little foundation. You've filed patent applications and secured patents, correct?

A Yes.

Q And you understood the way you get a patent is by filing an application and there proceeds a give and take with the patent office where letters are exchanged back and forth and ultimately the patent issues, right?

A I usually don't do that. Lawyers do that. I

work with them.

Q But you're aware that that process occurs?

A That happens, yeah.

Q Did you review any of the materials of that process, the give and take with the patent office, in getting the `338 patent?

A I don't think I saw anything there that was like between a lawyer and the patent office. I may have. I may have forgotten that, but I don't think so. I think mainly I heard -- I read about other people's, you know, like I'm talking about other expert witnesses or whatever.

Q Okay. But --

A I don't remember seeing documents like directed to the patent examiner by a lawyer, but that doesn't mean I didn't see them. I just don't recall any.

Q Okay, fair enough.

Now, again, just trying to establish the playing field that we're on here, is it your belief that you have expressed in your report all of the bases upon which you base the opinions that are expressed?

A All of the bases under which I expressed -- sometimes I just expressed my opinion without saying where it came from, I think. I mean, I'm not trying to be contrary here, but I don't understand what you're

asking me.

Q I mean, as I read your report, you state a series of opinions --

A Yes.

Q -- that bear on this issue of what is covered and what is not covered in the patent, and then you give a textural explanation for why that is your opinion. Is that a fair characterization of the structure of your report?

A I guess that's a fair characterization.

10:37 Q What I'm trying to find out is in the discussion portion of your report, have you stated all of the bases that you intend to rely upon to support the conclusions that you've given in the report?

A I would say no, because, I mean, my -- it's hard to like compartmentalize all of the information that I might bring to bear on the decision, you know, or

10:38 an opinion in this thing, because it's my whole professional lifetime of experience that really -- I didn't describe every single thing that I happened to know or that, you know, that I would use in my -- in -- I don't think that way. I don't say, "Because of this and this and this, these are all of the things that I know in that, I think this."

Sometimes with an issue as large as, like, the

specificity of various amplification techniques, I'm drawing on a lot of experience that I haven't really got the piece of paper -- a piece of paper in hand that I can say, "Here is why I know that." But I can talk about it at length if somebody wants to ask me why I have a particular opinion, and I can think through a lot of reasons that I have that particular opinion. I don't make up opinions, but I don't base them on specific little pieces of information all the time either.

I don't exclude that, but you're asking a question, is that all that I have drawn on to make these conclusions? I'm not in a position to tell you everything that I have drawn on. Not that I haven't drawn on something, but I just don't remember exactly where I learned each little thing that I know about this field.

If you can be really specific, I'd make a better answer to that question. If you say, "Where did you get your ideas for this particular statement that you made? Where did that come from?" then I can talk about it at length.

Q Sitting here today, are there reasons why you expressed the opinions you expressed in this report that you considered at the time and did not include in the report?

A No. Okay, I sort of understand what you're saying. Not consciously, I did not leave something out that I really thought was pertinent. I spoke freely and of my opinions and why I have them and so forth. I wasn't covering anything or hiding anything or trying to dodge any issues.

10:40

Q When did you first have occasion to read the Collins `338 patent which is the subject of your report?

A I think that was one of the first documents that I was sent, and I really -- like I said, I'm not sure when that happened, but I bet it was a year ago at least.

Q But to your knowledge that was the first time the Collins patent had come to your attention?

A It wasn't a big shocking patent. It didn't suddenly -- no, I would not have read it except for this case.

10:40

Q Now, in your experience, professional experience reflected in your CV, was there ever a time when you were involved in the development of diagnostic assays?

A Yes.

Q Can you briefly describe when and where that was and what the general nature of the activity was.

A Well, I think from the very beginning, developing PCR itself was -- you know, we started working with the first -- I mean, the first subject matter for use of PCR in anything more than just like model systems was analyzing for sickle cell anemia trait in DNA sample from a human. I mean, starting human blood and working to the DNA and doing the amplifications, that was a diagnostic test. That was the whole intention of the thing.

Q That was in connection with your work at Cetus?

A Cetus and then continuing at like a place called Xytronyx down in San Diego, I worked on a test there for Pneumocystis carinii, the organism. I've worked on various amplification systems relating to human DNA sequences where there are polymorphisms in the population.

I've done that -- I've done that in, let's see, Burstein Technologies, I've worked on that problem. In my various consulting capacities to lots and lots of companies, that's very often the subject matter of what I'm consulting for is usually a company with a -- like a diagnostic test that they're trying to do or a procedure that they're working out to do lots of them.

Q Were any of the diagnostic tests that you worked on actually commercialized?

A PCR has been actually commercialized. You might look in a copy of Science Magazine or something, yes.

Q I mean in the context of the diagnostic test.

A Yes, like the very first application, using for sickle cell anemia was commercialized. And then a whole bunch of things. Like, I mean, I worked on the HIV testing like for the actual nucleic acid of HIV in blood for Speciality Laboratories in Santa Monica where I was -- I mean, I worked there about three days a month for a couple of years and helped work out the techniques there.

I also developed a method there for like rapidly purifying DNA out of a blood sample that could be used in -- in what was used in a lot of diagnostic tests.

Q In any of that experience relating to diagnostic tests, have you had experience in developing non-specific amplification techniques?

A No.

Q Lest I have asked the question too narrowly, in your professional work reflected in your CV, whether or not directed to diagnostic applications, have you had experience with non-specific amplification techniques?

MR. SWINTON: Vague as to "experience."

10:44

THE WITNESS: No. My experience in the diagnostic area originated with PCR, and I kind of never looked back at that point. I've never gotten involved in non-specific amplification techniques.

BY MR. LIPSEY:

Q Do you know any people who have?

A No. Do you? I can't find any. Actually, I

10:45 think I searched for that, just such a thing, and I can't find anybody that is doing that commercially.

Q Okay. I'd like to ask you a couple of questions about the development of PCR, and I know you've been through this a thousand times, and I'll try to keep it short.

I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 200 the

10:45 1985 Science publication by -- how do you pronounce the name, Saiki, and others including Dr. Mullis.

(Defendant's Exhibit 200 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Is Defendant's Deposition Exhibit 200 the first

10:46 publication describing PCR?

A You know what, that's what I said. There actually somewhere is an abstract that was published earlier, just a brief abstract of the human genetics

meeting in Salt Lake City, which, I guess, really constitutes the first publication. It didn't describe details of how you would do it, and it wasn't like a formal paper that was reviewed or something, just like a couple of paragraphs that said "We've done this thing."

Q Okay. What was the date of that, if you recall?

A I think that is September 1985. I don't think -- it's not listed in my CV because it's not really a paper. It's just an abstract.

Q To your knowledge, Defendant's Exhibit 200 is the first formal paper describing PCR?

A Right.

MR. SWINTON: Let me just assert an objection for the record, that there are some interlineations on Exhibit 200. Just so the record is clear, those, I assume -- you're not representing they were part of the original publication? They came in some process other than Dr. Mullis?

MR. LIPSEY: Obviously, if they've been marked in some way, I'm not suggesting that's the way it appeared in Science.

Q Now, how long before the appearance of this publication had you invented PCR?

A I consider the invention to have happened, you

know, before I ever got it to work, and that happened in about May or early June of 1983, the first time that I actually got it to work. So like I say, this is not only in my mind, but it actually was December of 19- December 16th, 1983. That's when I showed it to a patent attorney and said "Look at this."

10:48

Q And is it correct that you have been involved in working with PCR first with Cetus and then with others essentially continuously since December of 1983?

A Sounds kind of boring, yeah. I've done a lot of other things, but I've been constantly called on for, you know, advice in projects, and I've done a few of them myself.

10:48

Q I apologize for some of these questions, but as I'm sure you've run into with other lawyers, we are not as technically trained as you are, and things that are clear to you sometimes are not clear to us.

In looking through this paper, it appeared to me that the experiment had been done with a 1-microgram sample of genomic DNA. Was that right? And specifically I'm looking at the legend in Figure 2.

10:49

A Yeah, at that point that's what we were using.

Q How was that -- I didn't see in the paper any description of how that was prepared. Do you recall how that was prepared?

A I think at this point when this paper was published, that was prepared by -- in a large quantity, you know, from like a lot of -- probably from a human blood sample, something like that. It was not prepared by me. It was something at this point in my association with diagnostics, it was a tube in a refrigerator that somebody else had put there and said, "This contains 1/10 of a Microgram per milliliter of human DNA," something like that.

And we had several different -- we had some from cell cultures of human -- because there were a number of cell lines, one of which I can almost remember the number of it, GM 2064 something that did not have the hemoglobin sequences, didn't have beta globin in it.

We had that. We had a line that had -- that was homozygous for sickle cell trait -- it's coming back -- SC-1, that's what that was called. And there was a wild type that had -- that was a heterozygote. So that would have been not purified from blood. The DNA would have been purified from human cell cultures that people had grown large quantities of.

Q Well, whether it's from blood or cell cultures, how do you get the genomic DNA?

A There is many ways to do that. You know, at that point the technology that we would have used to

purify the DNA for this paper would probably have been a chloroform phenol kind of extraction, where you mix the cells with -- actually, back then, probably somebody would have broken open the cells in some kind of little grinding device first, and then that would have been extracted with chloroform phenol to remove proteins and lipids, and then the DNA would have been probably precipitated from the aqueous solution there with ethanol. I think that would have been the procedure back then.

We would have wanted -- in the work we were doing for this, we would have been started -- before we would have started the amplification process, we would have managed to make purified human DNA that had very little of anything else in it but DNA.

Q Okay.

A We had lots of time. We weren't doing -- we weren't setting up a diagnostic routine there. We were developing the back end of one, but the front part we weren't really working on at that point.

Q When you say purified DNA, it had all of the DNA, including the stuff you were looking for and the stuff you weren't looking for, but it had been purified so that it didn't have stuff other than DNA?

A Right. It wouldn't have had proteins. It

probably -- and I'm not certain in that particular of the samples, I think it didn't have RNA in them either. I think they had been destroyed by enzymes, but it was whole human DNA.

Q Okay. I'm sorry for that digression.

10:52 Now, how quickly did PCR catch on as an amplification technique after its publication around Christmas of 1985?

A I think by June there would have been about seven or eight other papers that other people had published by then. By the next December, there were probably 150 to 200, and then up in the thousands by the 10:53 next year, I think, and that's just my recollection. I may be foreshortening that a little bit because of my advanced age, but I think within about two years there were probably at least a thousand papers published using that for various things.

Q So I gather it caught on pretty quickly?

A It caught on pretty quickly, yeah. Especially after June, June is when I presented it to the Cold 10:53 Spring Harbor Symposium, and that was like a whole lot of molecular biologists that had plenty of things they could do with it.

Q That was June of '86?

A June of '86.

Q Do you agree that by December of 1987, PCR was the most commonly used in vitro amplification technique known in the art?

A Yes.

Q Now, is it correct that even as late at 1987, you didn't recognize the applicability of PCR to techniques where the target DNA had already been isolated in pure form?

A Didn't -- wait a minute, I thought I just -- I did -- it was applicable to things where the target DNA had been isolated. Will you repeat that question. It seems like you got it backwards or I did.

Q Well, let me get at it this way. I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 201 a copy of what appears to be a chapter out of Volume 155 Methods In Enzymology, entitled "Specific Synthesis of DNA in Vitro via a Polymerase-Catalyzed Chain Reaction," by Drs. Mullis and Faloona.

(Defendant's Exhibit 201 was marked for identification by the court reporter.)

THE WITNESS: That publication, by the way, was very slow coming out. That paper was completed probably a year before that hit the stands in a sense. That was a volume of a like a compendium kind of thing,

Methods In Enzymology. It doesn't come out monthly or anything like that. So the paper that -- that actually is a reworking of a paper that I submitted to Science and Nature, both of which publications rejected that paper, which was my original publication on PCR that later got published in Methods In Enzymology.

10:56

But it's not fair to say that that represents the state of the PCR technology in -- in the year or the month that that came out. It had -- that paper had sat around for a little while. Do you see what I mean? There were a lot of other papers out about PCR by that time, although that one was intended to be by me, the first one. It didn't work out that way.

MR. LIPSEY: Let's let the reporter mark it as Defendant's Exhibit 201.

10:56

Q In the first paragraph of Exhibit 201, starting at the end of the sixth line you state, "It is not necessary that the sequence to be synthesized enzymatically be present initially in a pure form; it can be a minor fraction of a complex mixture, such as a segment of a single-copy gene in whole human DNA." Do you see that?

10:57

A I remember writing it.

Q So at least at the time you wrote this, whenever that was, you didn't recognize the desirability

of using PCR in situations where the target nucleic acid was available in pure form, right?

MR. SWINTON: Argumentative.

THE WITNESS: The first reaction I ever did was on a nucleic acid in pure form. I may not -- the question is I didn't recognize the ability of PCR to amplify something that was already in pure form?

BY MR. LIPSEY:

Q Right.

A I certainly -- the experiments are in here. This experiment right here was done on a purified plasma. See that picture? I mean, the very first PCR reaction I ever did was on a purified plasma DNA. It wasn't on a human sample or anything like that.

Q So why --

MR. SWINTON: The written record ought to reflect that Dr. Mullis showed counsel the figure on page 337 of Exhibit 201.

BY MR. LIPSEY:

Q If you appreciated that, why did you make the statement that I read here, that it's is not necessary that the sequence to be synthesized enzymatically be present initially in pure form?

A Because it's not. You can start with a sample that is vastly impure, and I think in this paper I

showed that. Whole human DNA, you can use that, or you can use what I did in this experiment, a tiny little plasma that was completely pure. You can do it on either one.

If you're working out the details of how to set up a PCR reaction for the first time, which I was, in some of the experiments in here, of course I would start with a purified sample of DNA, a model system, and then I would try to see if that would work in a system where the DNA wasn't pure, like in a real system that you might have to work on in a real diagnostic experiment.

To say that it can be, it says it is not necessary that the sequence to be synthesized enzymatically be present initially in a pure form. It's not. It doesn't mean you can't start with something in a pure form. In fact, you can start with something that has been amplified already, and it's just one fragment.

Q So the ability to start with DNA that was not in pure form was a benefit of PCR but not a limitation on the application of its use?

A Right.

Q Okay. Sorry about that.

Now, the PCR amplification process that you invented or with respect to the PCR amplification process that you invented, all of the elements for its

implementation were available in the literature for years before you made the invention; is that right?

A For some little time, yes.

Q For 15 years, as a matter of fact?

A 15 years, it's -- yes, I think it's possible that the -- there -- you know, let's see from 15 years from 1983, that goes back to -- I'm not -- I think there was -- yeah, there were a few people in the world who had things like oligonucleotides, and there was a little bit of sequence known about natural DNAs, so there was -- it would have been possible.

It was a lot easier by, you know -- it would come -- after oligonucleotides became readily available in purified form and more and more sequences were being known, it made it a lot easier, but I think somebody -- you're talking about 1970, though. I don't -- 15 years.

Q Let's try to help you out a little bit. I don't want to quibble with you. Let me mark for identification as Defendant's Deposition Exhibit 202 a copy of an article by Dr. Mullis appearing in Scientific American in April of 1990.

(Defendant's Exhibit 202 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Exhibit 202 is an article you wrote, right?

A Yes.

Q And in the middle column at the end of the first complete paragraph, you point out that PCR lay unrecognized for more than 15 years after all the elements of its implementation were available, do you see that?

11:02

A Yes.

Q I gather you believed that to be correct at the time?

A I -- right. It could have been 14, could have been 15.

Q It was about that time?

A Right.

Q But notwithstanding that, you still got a patent on PCR, right?

A Well, having the elements available does not prevent someone from getting a patent on something. You can put the elements together in a novel way.

Q I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 203 a copy of U.S. Patent No. 4,683,202.

11:02

(Defendant's Exhibit 203 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Now, Exhibit 203 is one of the patents listed

on your CV that I think you said you reviewed in preparing your expert report?

A Yes.

Q Okay. And is it fair to characterize Exhibit 203 as the basic patent on the PCR process?

A Yes.

Q And I think you said in your expert report that PCR is a specific amplification technique; is that right?

A Yes.

Q And I think you also said it is an exponential amplification technique; is that right?

A Yes.

Q Would you turn to column 27 of the Exhibit 203, please.

Do you see there claim 1, and that -- can you tell me, after you've done the steps that are outlined there in claim 1, how many copies of the target polynucleotide do you have? You can take a moment to read it.

A You assuming you start with one?

Q Yes, assuming you start with one.

A I think these steps --

Q Why don't you take a moment and just read it to yourself.

A You go from one to four. It's taking you through -- it's starting with whatever this target was, it's making two -- making that into two things and then taking those things and making them into four things.

Q So at the end of the steps here in claim 1, you would have four copies of the target, is that right, assuming you started with one?

MR. SWINTON: Objection; legal conclusion.

THE WITNESS: I -- yes, that's the way I would describe it.

BY MR. LIPSEY:

Q And in claim 2, it says that one of the possibilities is to repeat steps B and C once; do you see that?

A Yes.

MR. SWINTON: Objection; misstates. It says at least once.

BY MR. LIPSEY:

Q If you repeated steps B and C once, how many copies of the DNA would you have at that point?

A Every time you repeat it, you double the number of copies, so you would probably -- if you did it one time, then you would get eight, so at least eight.

Q Okay. That's fine.

Now, one of the enzymes you contemplated for

use in the PCR process was the Klenow fragment of E.coli DNA polymerase 1; is that right?

A Yes.

Q And, in fact, that's one of the ones mentioned in claim 7; is that right?

A Yes, it is.

Q Now, when you used the Klenow fragment to do PCR, you can get some non-specific amplification; is that right?

A You can -- yes, you will get some non-specific. You don't intend to, but that's the way the universe works, particularly biochemical reaction.

Q I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 204 a copy of an article appearing in Science in January of 1988, authored by Dr. Saiki and Mullis and others.

(Defendant's Exhibit 204 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Exhibit 204 is an article you co-authored; is that right?

A Yes.

Q This appeared in Science in January of 1988, down in the lower left-hand corner?

A Right, yes.

Q Would you turn to the second page of the exhibit, please. In the left-hand column, starting seven lines down, it states, "Electrophoretic examination of the reactions catalyzed by the Klenow polymerase reveals a broad molecular size distribution of amplification products that is presumably the result of non-specific annealing and extension of primers to unrelated genomic sequences under what are essentially nonstringent hybridization conditions. Klenow polymerase reaction buffer at 37 degrees C." Do you see where I've read?

A Yes.

Q Okay. Is that the phenomenon of unintended non-specific amplification with Klenow fragment that you just mentioned?

A Whether it's intended or not, I mean, is hard. I mean, I knew it was going to be that way. We all knew it was going to happen, but it wasn't what we really wanted, which is what happens when you gets a hot mixture, you get a lot better specificity.

Q To use the hot mixture, you have to use a thermostable polymerase like Taq; is that right?

A Right.

Q Now, even with PCR, you get linear amplification of the original long fragment of target

DNA; is that right?

A The long fragments accumulate in a linear fashion because they're the product of the original template in the primers, so that's the same in every cycle.

Q Are there commercial products of which you're aware that employ linear amplification?

A I -- I don't think so, but I, you know, I may be failing to remember some particular product, but I know that it's -- it works a lot better if you have an exponential reaction. I can't think of anybody who has a product that -- you know, there is a lot of modern little techniques that just might have that involved. I know when you're trying to sequence DNA, at some point you want to inhibit the exponential reaction because you try to produce a lot of single stranded DNA to sequence, and in that part of the reaction, it becomes linear.

By then you've amplified up from a, you know, a -- you've usually amplified in an exponential process first, and then you take a little bit of that and start this process that only has one primer in it to generate single strands and you are making more. There may be even by now commercially available kits for doing just that and not amplifying prior to that because the sensitivity of detection has gotten so high that it's

not -- if you start with something that is fairly abundant anyhow, you maybe don't even have to do exponential amplification, but I'm not currently up with the very latest techniques in those big sequencing companies, so I'm not really certain whether they ever start from an unamplified sequence. They may. There is no theoretical reason why you couldn't.

Q So, I gather the difference between a linear specific amplification technique and exponential specific amplification technique is that in a linear technique, you would use a single specific primer whereas in the exponential technique, you need to use two or more; is that correct?

A I -- yeah, I think that's fair to say. If you -- you could make copies of a single strand with just one primer and every cycle you would get another copy, that would be linear.

Q Okay. Now, the basic techniques needed to do the individual steps of PCR were generally known in the art even at the time you filed your application for the patent, which we have here as Defendant's Exhibit 203; is that correct?

A Yes, in a general way. The actual specific times and temperatures and stuff that I used may not have been published somewhere, but the idea of -- in

fact, the reason we were making oligonucleotides in the first place was to bind them to single strands of DNA and extend them once, or either bind them and just define that strand on the gel or something. Those techniques were already -- there were several recipes available for extending an oligonucleotide on a template.

11:13

BY MR. LIPSEY:

Q But techniques for making oligonucleotide primers were known in the art even at the time of your patent application?

A Oh, sure.

Q And techniques for separating the strands of double stranded DNA were known at that time too?

11:14

A Yes.

Q And techniques for second strand synthesis starting with the primer were known at that time?

A Yes, techniques for extending a primer on a template were known.

Q Now, in your patent, Defendant's Exhibit 203,

11:14

you have a discussion of the use of PCR for detection techniques; is that correct?

A I think so, yeah.

Q Okay. And I can point you to it if you'd like. That discussion extends from about column 13,

line 4 3 over to column 15, line 37 or so. Do you see that?

A Okay.

Q Okay. Now, in that discussion of detection techniques using PCR, you did not describe the combination in a detection assay of target capture with amplification by PCR; is that right?

MR. SWINTON: Vague as to "target capture," best evidence.

THE WITNESS: In this discussion, I don't think I said anything about target capture.

BY MR. LIPSEY:

Q Okay. And indeed in the examples of your patent, you didn't say anything about the combination of target capture of PCR either, right?

A I don't think in any of those examples I was dealing with that issue at all.

Q And you expected that the claims of your patent wouldn't be limited just to the specific embodiments that you described in the text, right?

MR. SWINTON: Objection; legal conclusion, relevance, beyond the scope of his opinions.

THE WITNESS: My answer to that was, certainly I did think it was going to go beyond the scope of just the exact claims -- not the claims, but the examples

that I made.

BY MR. LIPSEY:

Q Indeed you said that in column 27 of your patent at about line 25, do you see that?

MR. SWINTON: Same objections.

THE WITNESS: I think it's customary to say something like that, yeah.

BY MR. LIPSEY:

Q Do you believe that your patent covers the use of PCR in diagnostic assays when combined with a preliminary target capture technique?

MR. SWINTON: Objection; legal conclusion, beyond of scope of his opinion, incomplete hypothetical.

THE WITNESS: I think it applies any time you use PCR under any circumstances. Doesn't matter what you've done before or what you do later.

MR. LIPSEY: Why don't we take a short break and get organized.

THE VIDEOGRAPHER: This is the end of tape number one of Volume 1. We're off the record at 11:17.

(Recess.)

THE VIDEOGRAPHER: This is the beginning of tape number 2, Volume 1. We're on the record at 11:25.

MR. LIPSEY: I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 205 a

copy of U.S. Patent 4,683,195 naming Dr. Mullis as a coinventor.

(Defendant's Exhibit 205 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Dr. Mullis, Exhibit 205 is another one of your patents relating to PCR; is that right?

A Yes.

11:26 Q This is one of the patents you identified as having been reviewed in the course of preparing your expert report; is that right?

A Reviewed, but not memorized.

Q Fair enough.

In this patent, Exhibit 205, the claims are directed to processes for detecting the presence or

11:26 absence of specific nucleic acid sequences in a sample using PCR, correct?

MR. SWINTON: Objection; legal conclusion, best evidence.

THE WITNESS: Would you repeat exactly what you said, detecting -- doing PCR for purposes of detecting, cloning, whatever else I think we've said.

BY MR. LIPSEY:

Q Well, if you take a look at column 40, you'll see Claim 1 is there, and basically whereas your other

patent, Exhibit 203, claimed basically the process of amplification using PCR, this patent, Exhibit 205, claims processes for detecting the presence or absence of at least one specific nucleic acid in a sample using PCR.

A Right.

MR. SWINTON: Same objections.

BY MR. LIPSEY:

Q Now, we spoke a moment ago about the fact that there is some non-specific amplification, even with PCR, and that is true with respect to the TMA process as well; is that right?

A Yes.

Q I'd like the reporter to mark for identification as Defendant's deposition Exhibit 206 the text of an article appearing in McGraw-Hill's Biotechnology Newswatch October 6, 1986, entitled "DNA cleavage adapter groomed for genetic diagnostics."

(Defendant's Exhibit 206 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Do you recall seeing Exhibit 206 before?

A It's not altogether novel, but let me just understand what this is. Okay.

Q The second-to-last paragraph of the article

attributes some quotes to you. Well, I guess let me get an answer. Have you seen Exhibit 206 before?

A I -- it seems familiar, but it's probably a long time ago.

Q Would you take a look at the penultimate paragraph on the second page where there are some quotes attributed to you. Do you see that?

11:30 A Yes.

Q Okay. The Mullis technique referred to there is a reference to PCR, is that your understanding?

A Yes.

Q And then you're quoted as saying "You do get a lot of other things replicating that you don't want, but the background is low enough to be readable." Do you see that?

A Yes.

Q Is it your belief that that's a correct quotation from you?

A Yes.

Q Okay. I'd like the reporter to mark for

11:30 identification as Defendant's Deposition Exhibit 207 a copy of an article appearing in the Cold Spring Harbor Symposium on Quantitative Biology from 1996 entitled "Specific Enzymatic Amplification of DNA In Vitro: The

11:31 Polymerase Chain Reaction."

(Defendant's Exhibit 207 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Exhibit 207 is another publication co-authored by you; is that right?

A Yeah.

Q Would you turn to page 272, please.

A Okay.

11:31 Q In the left-hand column at the end of that first incomplete paragraph, the statement is made, "As a further simplification, PCR amplification has been performed directly on crude cell lysates, eliminating the need for DNA purification." Do you see that?

.:32 A Yes.

Q Is that a benefit of PCR or a limitation on its use?

A That's the benefit of it. You can do that.

Q Now, working backward through the paper, if you turn back to page 270 -- and the actual discussion

11:32 starts on 269, and feel free to look back at that at the context -- but there in the first complete paragraph on page 270, there is an indication that -- of cloned DNA sequences that had been amplified by PCR, only about 1 percent of them had the DNA fragment of interest; is that correct?

11:33 A It says only about 1 percent of the clones hybridized to the internal beta globin probe. Let me make sure I understand what is happening here. Right, I understand what it's saying. It is saying basically 99 percent of the sequences that were amplified out of that were not exactly -- were not beta globin.

Q Okay. And you indicate here that those other sequences were presumably amplifications of other segments of the genome rather than the one you wanted; is that right?

A That's probably one of the worst cases there because the globin family is an enormous super family of many sequences that all have very similar but not exactly the same sequence, so it's a bad -- it's one of the worst. It just happens that is the one we first started working with, and it was an unusually -- we did better than 1 percent, but in that case, that was using Klenow and that was with that particular site.

Q Over in the right-hand column on page 270, there is another experiment described where 80 percent of the cloned fragments that had been amplified with PCR were not the correct fragment; is that right?

A Right.

Q And your statement at the time about the cause of that was, "At this time the basis for the difference

in the specificity of amplification defined here is the ratio of target to nontarget clones is not clear but may reflect the primer sequences and their genomic distribution." What does that mean?

11:35 A That means the sequences, like the beta globin, the target sequence for beta globin is one of a super family of similar genes, and those primer sequences that were intended, they only occur once in their actual sequence, but there are several variations of them in various other places around the genome.

So the sequences that we chose to amplify, that 110 I think it was, were present in lots of different locations due to -- I mean, similar sequences to them were. So that's were the 1 percent -- I was trying to explain the difference between the beta globin case where you get 1 percent and the HLA-DQ alpha case where we got 20 percent.

And the HLA-DQ alpha is a very much more unique gene sequence than is the beta globin. So we were speculating at that point, and that's all we could do, but it looked -- it seemed reasonable that is what was going on.

11:36 Q So, one of -- the solution that you propose in this article for dealing with this amplification of something other than the target was to use nested sets

of PCR primers; is that right?

A Right.

Q Okay. And by that, you mean using four or perhaps even more primers instead of two in order for the PCR reaction to amplify only the target that you're interested in?

A Right. In effect, it's like you're doing two PCR reactions in a row. One of them you're doing on the whole human DNA, and then the other one you're doing on the product of that first one, which is now greatly -- although there's only 1 percent of beta globin in there, that compares to like 100,000th of a percent that was in there in the beginning, so it's relatively enriched.

And then after another level of that with the second set of primers, it goes up to a pretty much homogeneous sample, as you can see on the gels there.

Q And earlier in the paper, back on page 265, down on the bottom of the left-hand column, you indicate down there that sometimes PCR produces a molecule exclusively representative of the intended target and sometimes it does not.

MR. SWINTON: I'm sorry, direct me where it is.

MR. LIPSEY: It's in the lower left-hand column, under the heading "Nested Primer Sets."

THE WITNESS: On page --

BY MR. LIPSEY:

Q 265.

A 265.

MR. SWINTON: I'm going to ask, somebody has got to reread that, either you read it or the court reporter.

MR. LIPSEY: I'll do it.

Q At page 265 of Defendant's Exhibit 207, in the lower left-hand corner, you indicate that sometimes PCR produces a molecule exclusively representative of the intended target and sometimes it does not; is that right?

A Yes.

Q And that's a reference to the phenomenon that we just talked about that was discussed over on page 270; is that right?

11:38

A Right.

Q Okay. Now, in your expert report, you indicated that the problem with non-specific amplification was that it amplified all the other junk in the sample along with the target so that you never found the target. Is that a fair summary of one of your objections to non-specific amplification?

11:39

A Well, I don't remember using the word junk, and I don't remember the -- using the expression never found

the target. The target was not the only thing on the gel, and sometimes -- I mean, that's what some of the -- this process of nested primers was directed to that as a problem and solved it.

11:39 Is there any doubt in anybody's mind that the PCR reaction does not necessarily simply amplify one single molecule exactly, that there are other molecules that are similar that also get amplified? I think that's what I'm saying right there, right?

Q I was actually moving on to a different topic.

A Okay, well, move on.

Q I'm sorry, maybe we ought to take a look at your expert report so that we don't get confused. If I .:40 can find your expert report. Your report is marked as Exhibit 198. Do you have it?

A I think I probably do. Yes.

Q Would you turn to page 8. There you point out 11:41 one of the benefits of specific amplification, and PCR in particular, is the ability to find a needle in the haystack. Do you see that?

A Um-hum, yes.

Q And you indicate in contrast that non-specific amplification doesn't let you find the needle in the haystack because it amplifies something other than the 11:41 target DNA.

A The whole haystack.

Q I'm sorry?

A It just makes a new haystack with its own needle in it. It doesn't really give you an edge on it.

Q But the possibility of non-specific amplification in a PCR process can also make it impossible to find the needle in the haystack; isn't that right?

A The word -- using this word as two kinds of things, specific and non-specific, and in a verbal sense, that's true. But in an actual chemical reaction, there is many degrees of specificity, and PCR is much more specific than methods that aren't even designed to be specific, obviously. It's not absolutely specific. Even if you started with just one molecule of some pure substance, you would probably get a couple of misprimings and some things that you weren't intending to get because that's the way stochastic kind of biochemical reactions happen to work.

It's very different than somebody just -- like a carpenter doesn't make that kind of mistake. He makes a chair, he makes a chair. He doesn't make five things that look kind of like chairs and one that does.

But that's the way biochemical reactions are. It may be a little confusing to say this is specific and

this is non-specific. Like everything to some degree is non-specific, but the level of that can vary over like a factor of a billion or 100 billion fold, so you have to be -- I mean, there are shades of meaning all the way out from just a little bit more than random to extremely specific, and the extremely specific amplification reactions is why people got all excited, not the ones that that were non-specific. No one got excited about that.

Q Okay. But even in the case of PCR, it's possible for a non-specific amplification event to prevent you from finding the needle in the haystack; isn't that right?

MR. SWINTON: Incomplete hypothetical, assumes facts.

THE WITNESS: I -- even on the worst of days, I was usually able to find something that looked like it could be a bunch of different needles. But yeah, they can vary all the way from being very non-specific to very specific, depending a lot on the target you're looking for in the first place, its initial frequency, the -- your choice of the primers, whether you got lucky and hit some very unique sequences, whether you're doing the reactions at a very high temperature and being careful with not having any primings happening at low

temperatures.

You get the whole range of possibilities. With PCR you do have the possibility on one end of basically ending up with a gel that looks like there is just one thing on it, and that is sort of the definite, sort of the thing that got people excited about PCR. If you look back at those gels in the early days when we didn't have Taq polymerase and we were doing them at room temperature, there was a lot of different things on a gel where you were hoping to get just one band, but you knew you were going to get a lot of stuff. But you still got a selective amplification of that one thing, like it maybe got purified by a factor of say a million.

11:44

11:45

Q But it is still possible with PCR, because of non-specific amplification events, to end up with a gel that has just one thing on it that isn't what you're looking for, right?

MR. SWINTON: Incomplete hypothetical.

THE WITNESS: I don't know whether I ever had that happen where it just has one thing on there that wasn't -- I don't see how you can get that to happen actually. Can you find an example of that somewhere where you got one band and it was the wrong one?

MR. LIPSEY: Funny you should mention that.

I'd like the reporter to mark for

identification as Defendant's Deposition Exhibit 208 an article published in 1990 by Dr. Mullis entitled "Target amplification for DNA analysis by the polymerase chain reaction."

(Defendant's Exhibit 208 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Okay. Is Defendant's Exhibit 208 an article written by you?

A Yeah, I think this is probably, it was either -- yes.

Q What was the journal it appeared in?

A I'm trying to figure that out. It's got a -- some French thing because it has an abstract here. First Congress on Advanced Concepts in Biology in Paris, I guess it's a journal that is published by -- or maybe like a symposium kind of volume.

Q There is some abbreviation in the lower right-hand corner of the first page. I'm just not familiar with it. Do you know what that is?

A First Conference of Advanced Biotechnology, Paris. I don't remember it exactly.

Q On the right-hand side of the page.

A Oh, Annals of Biologica Clinica, 1990, okay, right.

Q What journal is that again? I just wasn't familiar with the abbreviation.

A I'd say it's probably in French right, it's probably Annalia Biologica Clinica (phonetic), something like that, it's just abbreviated there. It doesn't have a name.

Q Now, would you turn to page 582, please. There in the paragraph bridging the two columns you talk about some of the problems that arise by doing PCR at lower temperatures. Do you see that?

A Right.

Q And you state "By doing so, you generate a large number of incorrect extension products with the promiscuous oligomer at one end. Some of them, especially the long ones, will provide a site for a second primer to bind, and then you can have a fragment which can be amplified. But it isn't the one your grant was written about." Do you see that?

A Yes.

Q When you say "it isn't the one your grant was written about," you mean it's not the DNA you were trying to amplify in connection with the research grant that --

A Right, in other words, I've said this in sort of tongue in cheek, but it is possible that there is an

amplification product there that is not the -- the sequence is not exactly what your sequence is, but there is maybe a lot of it there to start with, and so your sequence is kind of lost. It doesn't get amplified. But I'm not recommending that as you'll notice. I'm saying that's if you did it all wrong, if you're running the reaction and you let it sit on the bench at room temperature for a while, I wouldn't consider that to be an intrinsic limitation of PCR. It's one way that it can go wrong, and it's suggesting how to avoid that here in this paper. Not saying that's the way it usually happens.

Q You go on to say, "Enough of these voluntary fragments can choke a PCR reaction to death at the level of the finite supply of polymerase before the intended target has been amplified to the level required by your detection system."

A Certainly can. And this is -- I mean, like I'm saying, it's not an intrinsic limitation on the reaction itself, as there are solutions to that, but even if the -- if you're trying to amplify something that is like one part in like 40 quadrillion or something, which is sometimes -- that's not an imaginary number when you're looking for a single sequence of, say, HIV DNA sequence in the presence of like 5 milliliters of blood,

and all of the DNA from it, you -- I mean, there, you can get a lot of -- sometimes, I mean, if you do the reactions in the cold and you're looking for such a tiny thing, your product is going to get amplified by the other things in there, so many other things in there, they're going to get amplified to the point where they just sort of just drown it out.

I think if you read this carefully, you'll see we're talking about real extreme cases, where even in those extreme conditions, there are remedies for that. The reaction can be extremely specific, and it's intended to be specific. It's not intended to work like that. It's just sometimes if you really pile up a lot of things against you, make it as hard as possible just for the sake of doing that, you can make it almost impossible to see the target you're looking for. But in the context of the way you said that, like something comes up that is the wrong thing and that is the only thing you see, that's not -- that's not generally the case. That's like the extreme.

Q Okay. But it was an event that was sufficiently probable that you felt the need to counsel readers about it in this publication in 1989 or 1990; is that right?

A It was an event that I felt was not

necessarily -- it was necessary -- I mean, I wrote the paper about it. I spent a long time, in fact, developing techniques to avoid it, and then I reported those techniques here.

Q Okay. I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 209 a publication by Dr. Mullis appearing -- published by the Cold Spring Harbor Laboratory Press in 1991 entitled, "The Polymerase Chain Reaction in an Anemic Mode: How to Avoid Cold Oligodeoxyribonuclear Fusion."

(Defendant's Exhibit 209 was marked for identification by the court reporter.)

MR. SWINTON: He always smiles when he gets the tough words right.

BY MR. LIPSEY:

Q Exhibit 209 is another article that you wrote; is that right?

A Yes.

Q And you make reference here to the problem when conducting PCR of getting I think what you called ugly little fragments, right?

A Yes.

Q And the ugly little fragments are the ones that arise from unintended priming events, right?

A Yes.

Q And you indicate that those ugly little fragments can be a particular problem -- or let me rephrase that.

You indicate that those unintended priming events can be a particular problem when you're looking for a needle in a haystack, right?

A Yes.

Q I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 210 a copy of an article by Dr. Mullis and others with the first named author being Kwok, K-w-o-k, appearing in the Journal of Virology May 1987.

(Defendant's Exhibit 210 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Exhibit 210 is an article co-authored by you; is that right?

A Yes.

Q And is this one of the articles you indicated that you looked at in the course of preparing your expert report?

A Yes.

Q And this article was published in 1987; is that right?

A Right.

Q And it relates to development of an assay for AIDS; is that right?

A Well, for the HIV virus. I don't think it was for AIDS.

Q And that assay employed PCR amplification; is that right?

A Yes.

11:55 Q Okay. But the assay described in this paper didn't combine the step of target capture prior to amplification; is that right?

MR. SWINTON: Vague as to "target capture."

THE WITNESS: As far as I remember, we weren't doing target capture.

BY MR. LIPSEY:

Q Okay.

A I think we were doing analytical work on the 11:55 back end to try to see if we were looking at -- here again, we were looking at trying to find one tiny thing in the presence of a lot more than just like one gene in a human gene -- we were looking for a viral gene that could be there. Nobody wanted any of it in their blood, so if you take a 5-milliliter blood or a milliliter sample, you want to say there is not a single one in there. So this was pushing the technology, and it was pretty early in the -- it was 1987, so --

Q I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 2 -- strike that.

I'd like to show you a copy of a document that has previously been marked for identification as Plaintiff's Exhibit 5 in this action, which is the `338 patent.

Okay, now, I think you indicated in your expert report you had read the text and claims of the patent; is that right?

A Yes.

Q Okay. On the first page of Plaintiff's Exhibit 5, there is an abstract, do you see that?

A Yes.

Q Okay. It says "A method of assay for target polynucleotides includes steps for isolating target polynucleotides from extraneous non-target nucleotides, debris and impurities and amplifying the target polynucleotide." Do you see where I'm reading?

A Yes.

Q There is no reference to non-specific in that sentence, is there?

MR. SWINTON: Best evidence.

THE WITNESS: It doesn't say anything at all about the specificity of the amplification. That is an

abstract, however.

:58 BY MR. LIPSEY:

Q Would you turn to column 2 of the `338 patent, Plaintiff's Exhibit 5. See there starting at about line 9 there is a definition of the term amplify?

A Yes.

Q And there is no reference in that definition to non-specific amplification, correct?

A Let's see, I think the guy that wrote this had

11:58 better vision.

Q Certainly the guy who printed it.

A Right. And the question you had was there is no reference to the specificity in that?

Q There is no reference to non-specific amplification in that definition in column 2, is there?

11:59 MR. SWINTON: Same objection.

THE WITNESS: I don't see any part of that that is directed to specificity. It doesn't say anything one way or the other. There is nothing in the first paragraph right after background of the invention about it either, but it doesn't really prove anything, does it?

BY MR. LIPSEY:

Q Would you turn to column 9, please. And there

11:59 starting at about line 42 the text states "The invention

also features a method for assaying a sample for a target polynucleotide which sample contains the target polynucleotide and non-target polynucleotides. The method involving contacting the sample with a polynucleotide probe capable of forming a complex with the target polynucleotide, substantially separating the complex from the non-target nucleotides in the sample, amplifying the target polynucleotide, to form an amplification product and measuring or detecting the amplified target polynucleotide." Do you see where I've read?

A Yes.

Q There is no reference to non-specific amplification there either, is there?

MR. SWINTON: Same objection.

THE WITNESS: Notice, again, the author is not -- he has not gotten into that issue in any of those places. The answer is no, it doesn't say anything about it, as I'm sure you checked before you read it.

BY MR. LIPSEY:

Q Just wanted to make sure. Would you turn to column 15, please. Starting at about line 39 it states, "An embodiment of the present method can" -- should say be -- "practiced with additional amplification steps to generate an amplification product to improve the

sensitivity of the assay." Do you see where I've read?

A Yes.

Q There is no reference to specific amplification -- excuse me, there is no reference to non-specific amplification in that sentence, correct?

MR. SWINTON: Best evidence.

THE WITNESS: None.

BY MR. LIPSEY:

Q I'm sorry?

A I don't see any. I mean --

Q Okay. Turn to column 30, please. Starting at about line 15 the text states "The sensitivity of the above DNA or RNA target capture methods can be enhanced by amplifying the captured nucleic acids." Do you see where I've read?

A I see what you read, yes.

Q There is no reference in that sentence to non-specific amplification, correct?

MR. SWINTON: Same objection.

THE WITNESS: In that -- he is not talking about selectivity there. He is just talking about sensitivity.

BY MR. LIPSEY:

Q There is no reference to non-specific amplification, is there, in that sentence?

A Well, the next sentence takes up the question, again.

Q But in that first sentence, there is no reference --

A It says, "This can be achieved by non-specific replication using standard enzymes." That's the sentence referring to that sentence that you read, the very next sentence.

Q The first sentence of the paragraph says nothing about non-specific amplification, correct?

A You're not supposed to read one sentence in a patent and take it out of context unless you're a really, you know, disgraceful patent lawyer, you read the whole things. The very next sentence talks about non-specific amplification, doesn't it? And is says the way you would do that is by non-specific replication using standard enzymes.

So it's kind of -- it has no meaning at all to say this one sentence there is no reference non-specific amplification, where if, in fact, in that same paragraph that sentence is referred to with a description of sort of a further description of what he is talking about and it says non-specific.

Q We'll come back to that in just a minute because I know you have some views on that and I'd like

to hear what they are.

Would you turn to column 32, please.

Do you see there in Claim 1 talks about a method for amplifying a target polynucleotide? Do you see that?

A Yes.

Q And step C is amplifying the target polynucleotide?

A That's right.

Q There is no reference to non-specific amplification there, is there?

MR. SWINTON: Same objection.

THE WITNESS: Not in 1 (c).

By MR. LIPSEY:

Q Okay. Now, going back --

A I think it's common for claims to refer back to the examples in a sentence. You're supposed to interpret the claims in light of the examples and also the specifications. They don't stand by themselves. There is no way to understand what he is talking about right there without looking back at the rest of the patent to find out what he did.

Q Okay, let's go back and talk about that.

Let's go back to column 30 of the `338 patent, Plaintiff's Exhibit 5. And specifically to the

12:04 penultimate sentence before example 4, starting at about line 38. The text states there "Thus no specially tailored primers are needed for each test and the same standard amplification reagents can be used regardless of the targets." Do you see where I've read?

A I see it.

Q You understood that reference to specially tailored primers to be a reference to specific primers of the sort used in specific amplification techniques,

12:05 correct?

A Yes.

Q And further up, starting at about line 32, well, starting at line 30 it says, "Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ non-specific enzymes or primers." Do you see where I've

12:05 read?

A I see that.

Q The alternative to non-specific enzymes and primers is specific enzymes and primers, correct?

A Well, you might have non-specific enzymes and specific primers or you could have a lot of other alternatives, but that is one of them.

Q Okay. Now, I think in your expert report you

12:06 indicated that it can be an awful lot of work to

actually design a specific primer for use in PCR; is that right?

A Did I say it would be an awful lot of work?

Q Could be an awful lot of work.

A I'd like to see that. I don't remember doing an awful lot of work to do that. It's a process that is pretty much done by computers now. Did I say --

12:06 Q Would you turn to page 11 of your expert

12:07 report, Defendant's Exhibit 198, please.

You're talking about in the first paragraph about the process of designing primers for use in PCR. And you indicate all of the factors that need to be taken into consideration in designing that primer, do you see that?

A Right.

Q And then you say it's common for scientists to

12:07 design, test and then redesign and retest sequence specific primers?

A If you're setting up a -- if you're going to set up reactions, as you do very often, you want to optimize all kinds of things. That would be one of the things you -- I didn't say anything about a lot of work there.

Q I mean, in fact, some of your early experiments failed because you hadn't properly designed the primer,

right?

A Well, which of my experiments failed? I'm not sure what you're talking about here. Failed in what sense? Failed in not amplifying the things that I wanted?

Q Right.

A The only one I think we've seen reference to where it didn't get the needle in the haystack thing is where I was running the reaction -- I was suggesting don't run it at a cold temperature, you're causing -- you're shooting yourself in the foot. But there is no doubt that you can have better and better specificity by finding just that right combination of primers. I didn't say anything about how much work it was. But, I mean, you can, you can spend a lot of time on it if you want to. Usually the first two you pick work.

Q Well --

A That's usually the case.

Q Well, which is it? Is it a trivial matter?

A Usually the first two that you pick work, okay? If you're going to be doing a reaction many, many times and you want to find the very best set of primers, then you could -- you can shop around and find different ones and say -- compare them all to each other and say which is the best.

And that's what you would do if you're setting up like a routine laboratory procedure for, you know -- like if you're looking for some organism that is going to happen -- that you're going to have lots and lots of applications for that particular thing, then you might spend a lot of time doing it. Usually the first pair of primers that you pick, however, get you a result that will be useful in that -- in the average situations.

People don't spend a lot of time. They have little computer programs that basically try to match the melting temperature of both primers by using the little equation that gives you that, and if you -- you put a pair of primers together and they don't give you the result that you're wanting, that is usually the exception, and then you might want to alter them because maybe those primers are amplifying a sequence that actually has those primers in it, but you just didn't know about that sequence. That sometimes can happen.

There is not a lot -- there is nothing in there that says it's a lot of work. I believe you were saying it was a lot of work.

Q You did not mean in the sentence where you wrote, "It is come on for scientists to design, test and then redesign and retest sequence specific primers to achieve effective sequence specific amplification of a

desired target sequence," you did not intend by that to suggest by that it was a lot of work; is that your testimony?

A Actually, I'll read you what I said. I said, "Designing specific primers requires some knowledge of the intended target sequence," okay, that's not a lot of work yet, is it, "and often requires laboratory testing to determine if the sequence specific primers, in fact, function in a sequence specific manner to amplify the intended target sequence."

So you have to do an experiment. That's what you're going to do anyhow if you're going to use them, right? And if it works the first time, no work has actually been expended selecting targets. If you want to optimize a reaction for more and more strenuous conditions, you might do a little bit more, you put a little more effort into that.

But I'm not sure what the point is that you're trying to make. Is it -- you know, when this patent was first applied for, you could say, hey, it takes a lot of effort to synthesize oligos. It is not the way it is now, and it's not they way it was when I wrote this.

Q By "this patent," did you mean your patent?

A No, the `338 there, those people felt like there was a need -- that it was -- they thought it was a

real pain to have to synthesize primers. They also were operating under another constraint, we might add, in that they knew they couldn't get away with using two specific primers because that was already patented. So they were trying to get around that patent by saying here is another way to achieve the same result as PCR does without doing PCR. That is the intention of these people.

And then they say, "Now, well, look how cool this is," they have to show utility, so they say, "Here is a way to do that without even having to synthesize the primers." But we know what they're talking about, don't we?

Q Well, let me -- let me --

A Were they suffering from having to synthesize primers, or were they just trying to come up with another way to amplify sequences that wouldn't be subject to the `202 patent? That's what they were doing. They weren't having a problem synthesizing oligodes by then. There were machines.

Q So a benefit of combining target capture with amplification is that it becomes possible to do an assay that doesn't infringe your patent?

A Theoretically, although I have not seen any --

MR. SWINTON: Vague -- I'm sorry, vague as to

the definition of "amplification." Incomplete hypothetical.

MR. LIPSEY: You may answer.

THE WITNESS: Repeat the question again because I want to make sure of what you said.

BY MR. LIPSEY:

Q So a benefit of combining target capture with amplification in an assay is that it becomes possible to conduct that assay in a way that wouldn't infringe your `202 patent, right?

MR. SWINTON: Same objection.

THE WITNESS: I think that was the point here was to try to figure out a way to amplify -- although we also know it didn't work. But Amoco is used to dry holes, aren't we? I mean, it didn't work in any practical sense. It said it did, but it didn't. Nobody has used it.

BY MR. LIPSEY:

Q Well, have you done any experiments? Have you duplicated any of the experiments in the patent?

A No.

Q Do you know anybody that has?

A I don't know anybody that does non-specific amplification now for a living.

Q Okay. That --

A Can't find anything in the literature about that.

Q We've covered a lot of ground here. I want to touch on all of it, but let's do it in a systematic way. Let's go back to the paragraph on page 11 of your report, Exhibit 198.

In that whole discussion of the process of designing primers and figuring out what the reaction conditions and what not are, under which they'll hybridize, were you meaning to suggest there that that process was beyond the capabilities of people working in this field in December of 1987?

A Well, it was harder than it is now. Now you're just -- you get a computer program, there is computer programs freely available on the net that do that all the time. What are you -- I'm not sure what your question is, we did that in a sense, but not as well as we can do it today because we have more sequences available.

Q But the experimentation needed to make the primers and get them to work is something that people knew how to do in December of 1987; is that right?

A They didn't always know exactly what all of the factors were, but they knew how to do the experiments empirically and test a set of primers in the situation

that they would be used and find out whether they worked.

Q Okay.

A We did that.

Q Okay. Fair enough.

And, in fact, that's something you have to do in order to do PCR each time also, right?

A You have to get -- use the right sequences of your primer. You have to know the sequences you're going to amplify. That kind of goes without saying, doesn't it?

Q Now --

A Things like oligonucleotides melting temperature, sequence composition, those are things that weren't all that clear in 1987 but have come clear since, and they're now approached with computer programs that can calculate melting temperatures and get the both primers matched up. You also have access to the database, the human genome, so you can look and see if there are other fragments that might amplify with those.

Q But those matters going to questions of primer design and selecting hybridization conditions were sufficiently well known in December of 1987 for people to do PCR, right?

A Yes.

Q Now, let's take a look at Example 5 of the `338 patent, which is Plaintiff's Exhibit 5. Why don't you take a -- well, you've read this and read it recently, I gather; is that right?

A I haven't read it recently. I read it some time ago.

Q Why don't you take a moment and read it.

A Okay.

Q Okay. Now, in that example, once the denatured target DNA is isolated and then made double stranded, the RNA polymerase basically functions to make many copies of the RNA transcript of that DNA, correct?

A Right.

Q And one way of making that isolated denatured target DNA double stranded described here is by use of random primers, right?

MR. SWINTON: Objection; argumentative, vague as to "one way." The document speaks for itself.

THE WITNESS: One way to attempt to do that would be to use random primers, although that's -- it's kind of strange that they say that makes it double stranded because most of it still ends up being single stranded. It doesn't work the same way when do you it with specific primers as it does when you do it with non-specific ones, because it makes many different

molecules that overlap sometimes and become double stranded but which have not the same ends necessarily. Do you see the difference there.

That gives you some double stranded character, which they in this case would like to have because the RNA polymerase in their eyes only acts on double stranded sequences, but they're wrong there too because it will act on a single stranded sequence, but that's what they're trying to accomplish.

Q Okay. The example goes on to state, "Alternatively, the double stranded DNA can be formed by synthesis starting from Capture Probe A," do you see that?

A Yes.

Q Now, Capture Probe A is a specific oligonucleotide primer, correct?

A Yes, that's the one they wanted to use for the probe.

Q So if one follows that approach, then the only double stranded DNA in the system is DNA to which that capture probe specifically bound, correct?

MR. SWINTON: Incomplete hypothetical.

THE WITNESS: Yes. It actually -- to do it this way would probably lead to more specificity than to do it with the random hexamers. You've already got it

hanging there, you might as well extend it on them. As long as you don't do it twice, you don't get in trouble with the '202.

BY MR. LIPSEY:

Q What do you mean by that?

A Well, if you put another primer on the other end and do it, do it again with that one, now you've got PCR.

Q But, in fact, you could do it repeatedly with that single capture probe and get specific linear amplification, right?

MR. SWINTON: Argumentative --

THE WITNESS: Specific, in the sense of more specific than doing it with the hexamers, but certainly not specific in regard to -- with respect to doing it with two different oligos that both had to be involved. That's a very big difference. It's a difference like 10 to the 7th and 10 to the 14th, which is a big difference. It's lots of zeros. That's why I was talking early there are levels of specificity, and certainly, this particular example would lead -- would probably lead to a more specific -- a more specific amplification than just the one where you know for sure it isn't specific.

This one, also, you could repeat, like you're

saying, you could do it, melt it off, do it again, melt it off, do it again, and you would get a linear amplification that was more specific than just amplifying everything.

BY MR. LIPSEY:

Q If we now look at Example 7, why don't you take a moment and look at that again. This is in the `338 patent, Plaintiff's Exhibit 5.

12:22 A You want me to read the claims?

12:22 Q No, just Example 7.

A Okay. I'm done with that.

Q Okay. There is reference there to an in vitro exponential amplification method.

A The Q-Beta-replicase things, right.

Q But the property of it is described as being in vitro, and it's said to replicate exponentially.

A Yes.

Q Now, if I told you in December of 1987 to use an in vitro method of exponential amplification, what is

12:23 the first thing that would have come to mind?

MR. SWINTON: Objection; incomplete hypothetical.

THE WITNESS: If you told me in 1987, what would come to my mind?

BY MR. LIPSEY:

Q Yes.

A I would say I do it every day.

Q PCR?

A Um-hum.

Q Okay.

A If you told me to use the Q-Beta-replicase to achieve it, I would laugh at you, however.

12:23 Q You would just look at that and know it wouldn't work, is that what you're saying?

A I would look at the -- at that point there was some literature available on Q-Beta-replicase system, and it never was practical to use it in any kind of a diagnostic situation. It was interesting from a molecular biological standpoint, looked nice on paper too, maybe to lawyers, but it didn't work. It didn't work for the purpose of making a specific target, making

12:24 copies of a specific target.

Q And --

A They didn't try to do that here either. They don't use the replication as a form of specificity. They just use it as a form of replication.

Q I mean, are you suggesting you could have looked at that thing in December of 1987 and known it wouldn't work?

A Q-Beta-replicase, to do a specific -- to

amplify a specific sequence, knowing what I knew in '87, the Q-Beta-replicase system had been around probably for about 10 years, but it was looked at as a -- people talked about it sometimes for its ability to amplify things, but people had not practically used it.

People, you know, had been working on the problem of trying to detect DNA sequences before PCR, and this was one of the things mentioned back there somewhere I'm sure in JBC papers and stuff, but not in a practical way.

Nobody around Cetus, for instance, who was working on this problem tried the Q-Beta-replicase thing before PCR, and they certainly wouldn't have afterward. But even before, when we were dealing with very low target levels, this -- that was a pretty fanciful way to go about it. It didn't work in the way -- it did not -- there was nothing in there that had to do with selectivity or specificity. It's just it had to do with total sample amount. There are two subjects, how much of it have you got, and is it in the presence of so much other stuff that you can't see it? Those are separate issues.

But the Q-Beta-replicase didn't really relate to the issue of how do you separate your particular sequence from all of the rest of them.

Q But if you could have separated your sequence from all of the rest of them, would you have understood the Q-Beta-replicase could have made many, many, many copies of that isolated sequence?

MR. SWINTON: Incomplete hypothetical, vague as to time, beyond the scope of his opinion.

THE WITNESS: I would have understood that it could have made a lot of copies of itself and some sequence attached to it, and there were technical difficulties there that I wouldn't have tried to use that. I would have tried to think of a better method, and I did. But, I mean, I don't know what you're trying to prove.

Are you saying if you had a single sequence and you somehow attached it, put it into the Q-beta system, then could that thing amplify just that -- it amplifies that, it also amplifies a lot of other sequences related to itself. You know, the Q-beta has to replicate its own self in addition to replicating the sequence that you've sort of fooled it with.

Q Okay. I'm actually just trying to get your view as to whether somebody reading that Example 7 in December of 1987 would have concluded that on its face it wouldn't have worked as described there.

MR. SWINTON: Objection; beyond the scope of

his opinion, incomplete hypothetical.

THE WITNESS: I don't know about somebody else, but when I see an example like that that doesn't contain any detail and no results, I would say I bet they didn't even try it.

MR. LIPSEY: That wasn't quite my question.

THE WITNESS: Well, I would have said it probably won't work either because I know about this. Here Blumenthal describing this when, '79? I mean, there was -- there were papers out there about the Q-Beta-replicase system because it was a curious thing.

MR. LIPSEY: Why don't we break for lunch.

THE VIDEOGRAPHER: Off the record at 12:27.

(Lunch recess.)

THE VIDEOGRAPHER: On the record at 1:26.

BY MR. LIPSEY:

Q Dr. Mullis, could you take out your expert report, Defendant's Exhibit 198, please.

A Okay.

Q Would you turn to the second page, please. There in the first paragraph, you refer to your understanding about the Doctrine of Equivalents, do you see that?

A Right.

Q From whence did you derive your understanding?

A From, I guess, Bill Bowen probably explained that to me.

Q Further down on the page under the heading "Nucleic Acid Amplification," you refer to probes there in the first paragraph, do you see that?

A Right.

Q In this field, I guess in December of '87, since that's the time we're talking about, when people referred to probes in nucleic acid assays, what generally did that mean?

A It's the same still. It would be like -- a probe for nucleic acids would be a complimentary -- nucleic acids was complimentary to a sequence that you were trying to detect, so it would attach itself specifically to it, and a probe usually carries some sort of signal, like it to could be a flourescent thing, or it could be radioactively labeled, something like that, so it allows you to locate and detect a particular sequence.

Q Would you turn to page 5, please. The third line there you state in part, "Generally practical in vitro amplification methods use two primers." Do you see that?

A Yes.

Q What are the alternatives to using two primers?

MR. SWINTON: Incomplete hypothetical, vague. Alternatives to what?

THE WITNESS: You know, I probably could have stated that a -- I could have said forget about the "generally." I could have just said "Practical in vitro amplification methods use two primers." So, I mean, you're asking me what else would there be and my -- I would have to say that there probably isn't any -- I don't know of any at least widely used other methods. So generally is maybe not the right way to phrase that.

BY MR. LIPSEY:

Q Well, I think we talked earlier about what happens when you use only one primer; do you remember that?

A You could use -- yeah, it's true, but there is like -- you could -- you could -- like to make a sequencing, like a template for sequencing, I think these days sometimes they don't amplify. First they do that sort of -- it looks like PCR when you're doing it, because you're doing it in one of their machines, but you only have one primer in there, and you just run about 10 cycles or 20 cycles, and it makes a single stranded template that makes it real easy to sequence.

Q In each one of those cycles it would make one more copy of the template?

A One more copy.

Q So at the end of the cycle, you would have 20 more copies of the template?

A I guess generally was the right word there --

Q I thought that was what you meant. I just didn't know if you had something else in mind.

Would you turn to page 6, please. Now, in this section of your report, you deal with the question of whether specific and non-specific amplification methods perform substantially the same function; is that right?

A Yes.

Q Now, in your discussion -- well, maybe we can short circuit this. Later on you analyze whether or not they perform in the same way. Do you remember that generally?

A Yes.

Q And then I think you talk about whether or not they obtain the same result later in the report.

A Um-hum.

Q In connection with all of those analyses, do you mention the impact of separating the target nucleic acid from other nucleic acids in the sample before amplification?

MR. SWINTON: Best evidence, irrelevant, beyond the scope of his opinion.

13:31

THE WITNESS: I'm not certain that I understand the question that you're asking me, so --

BY MR. LIPSEY:

Q I mean, it seemed to me reading your report that you were comparing and contrasting specific and non-specific amplification generally and not necessarily comparing and contrasting specific and non-specific amplification in the context of a process where the target nucleotide had already been isolated from the

13:32 sample; is that right?

MR. SWINTON: Same objections.

THE WITNESS: I may have been. I mean, I was talking about specific and non-specific amplification methods, and I was trying to describe what that meant and not the entire processes that might be used in.

BY MR. LIPSEY:

Q Okay. Would you turn to page 7, please. Now,

13:32 here we're still talking about whether specific and non-specific amplification performed the same function, right, that's the heading on the prior page?

A Um-hum.

Q And you state at the bottom, "If one amplifies

13:33 non-specifically the amount of the nucleic acid in the entire sample may have been increased to the point that it is impossible to analyze it, even if the amount of

the target sequence has been increased to detectable levels," do you see that?

A Yeah.

Q Okay. What did you mean by that?

A Well, if you -- let's say you're trying to -- you have a tube that has got, say -- maybe it's got a Microgram of DNA total in it, of which maybe a millionth of that or a picogram of that is the sequence that you're interested in. Now, if you -- if you need to have like, say, a thousand picograms of this sequence that you're interested in in order to detect it, and you try to produce that by making a thousand copies of every single thing that is in there, you're going to end up with a thousand micrograms of total DNA in the tube, and you can't put a thousand micrograms of total DNA on most of the detection systems that one would use to detect a thousand -- I mean, like a thousand picograms of a single sequence. It's just physically impossible.

So it says you could have it there, but you can't really -- you can't stick it -- you can't put it into a mass spectrometer, you can't put it onto an electrophoretic gel, you can't really probe it in the presence of all that DNA that you've made. You haven't really helped yourself a lot if you're trying to find something specific just by amplifying up everything in

general. That should be self-evident.

Q Now I understand what you meant.

I'd like the reporter to mark as identification Defendant's Deposition Exhibit 211 one of the documents that Dr. Mullis brought with him this morning, which appears to be a copy of page 7 of his expert report with some handwritten notes. I'm sorry, a copy of his declaration.

(Defendant's Exhibit 211 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q The paragraph we've been talking about in your expert report, Defendant's Exhibit 198, appears here as paragraph 20 of this declaration; is that right?

A Okay.

MR. SWINTON: Could I see the entirety of the document from which this was extracted.

MR. LIPSEY: Sure.

MR. SWINTON: Could you pull it out so I don't have to fumble through.

MR. LIPSEY: My fumbling is the same as your fumbling.

MR. SWINTON: If you're fumbling, at least you're not asking a question that I have to try to listen to at the same time. So one of us can't do two

things at once.

MR. LIPSEY: It's right there. In fact, if you would like to show the witness the original, I have no objection to that.

Are you ready?

MR. SWINTON: He has offered if you want to see the original, it's there. I've seen it for my purposes.

BY MR. LIPSEY:

Q Okay. Just to get us started here, this paragraph No. 20 on Defendant's Exhibit 211 appears to correspond to the paragraph on the bottom of page 7 of your expert report; do you agree with that?

A I think so. I mean, do you want me to read it?

Q I haven't read it word for word, but it --

A It ends and begins the same so hopefully the middle is the same too.

Q Now, the handwriting on the side of Exhibit 211 is whose?

A That's mine, and I think that was probably yesterday.

Q Can you read into the record what you've written there.

A "The chances of finding a needle in a haystack are not necessarily improved by multiplying the needle and the haystack to many needles and many haystacks,"

and then I said sort of a colon I think is that punctuation mark, sort of like saying thus, "non-specific amplification doesn't improve your chances of finding a needle in a haystack."

13:37

Q Okay. And that is, in more laymen friendly words, the point you were making in that paragraph 20?

A Right. If you're trying to find your car, for instance, in a big parking lot, it won't do you any good to have every car in the parking lot duplicate itself a few times. You still have to search through the same number of cars to find yours. But if you have your car duplicate itself a few times and the rest of the cars just stay like they are, you have a better chance of finding your car.

13:38

Q To stick with your needle in the haystack analogy, if you took the needle out of the haystack first --

A Then you've already found it.

MR. SWINTON: You have to -- I have an objection and we have to let him finish the question.

BY MR. LIPSEY:

Q -- and then multiplied the needle, you could help yourself out in terms of detecting the needle, right?

MR. SWINTON: Objection; relevance, beyond the

scope of his opinion, incomplete hypothetical.

THE WITNESS: I was -- I'm only talking about the amplification process itself. I'm not talking about some other way of specifically identifying the thing. If you want me to address that, I can. I mean, it is within my range of knowledge. I'm not saying that if you really could do that, that it might not work sometimes. In my opinion, actually, you know, the methods that are described in this patent, they haven't ever worked anywhere well enough to have been of note to anyone.

But I'm not saying absolutely that they wouldn't do something at some time. I'm not saying that. But I'm saying the amplification part of it, taken separately doesn't improve your chances just to make more of it, if you make more of everything that is in the way.

See, I mean, if you want to identify something in somebody's blood stream, right, that's a lot easier, there is nothing stopping you from taking 10 milliliters of blood instead of a tenth of a milliliter of blood. It's just that you don't really have any better chance of discovering some minute quantity of something in someone's blood by just taking more of it, because it's the background that is the problem, and non-specific

amplification doesn't solve that problem.

Now, if you can solve that with some other method, then maybe the non-specific amplification -- once you have the thing isolated by itself, maybe the non-specific amplification will help you bring that up to a level of detectability.

Although, as I mentioned before, when we started talking about where linear amplifications may be used right now, the limit of detectability these days is pretty low. So, I mean, non-specific amplification doesn't really have much role to play, as far as I'm concerned, in any -- didn't in 19- -- didn't in 1987 or whenever this thing was first patented, and it doesn't now. It's never been used because it doesn't. You're beating a dead horse here.

BY MR. LIPSEY:

Q How many copies of a target polynucleotide can you make using non-specific amplification, if you know?

MR. SWINTON: Incomplete hypothetical, beyond the scope of his opinion.

THE WITNESS: How many do I think you could make?

BY MR. LIPSEY:

Q Yeah?

A I really, like I said earlier, I haven't had

any direct personal experience with it, but it depends on -- you know, it depends on how small a fraction of the sample you're dealing with is actually the target that you're interested in. If it's very -- if it's a lot of it there in the first place compared to the background, then maybe you can do yourself some good by amplifying the whole mixture, maybe.

But as you -- every time you -- if you start -- think of a mixture might be a million different things. Every step of amplification is going to create another million things, right, instead of just another one or two or four or eight or whatever of the one you want. If you have to make a million every time, then you have two million things, and then have you to amplify.

Just to get another two copies of the thing you're looking for, you have to make four million things, and eventually that just fills up the space and uses up all the reagents. The enzymes can only work at a certain rate. You know, it just -- it's a losing proposition.

Q Would you turn to page 9 of your report, Defendant's Exhibit 198. You make the statement there in the bottom paragraph starting in the second line, that "TMA and PCR may result in some very limited amount of amplification of non-target sequences." Do you see

where I've read?

A Yes.

Q Do you have any information as to whether TMA is more specific or less specific than PCR?

A It's -- if PCR is practiced as is currently -- after about 1987 was with a thermostabile polymerase so the reactions can be run under very high specificity, TMA, in my experience -- which can't be because some of the enzymes are labile to heat -- is about a million times less specific.

Q And that's why Gen-Probe needs to use target capture prior to TMA amplification; is that right?

MR. SWINTON: Argumentative, lacks foundation, beyond the scope.

THE WITNESS: I wasn't involved in that work, so I'm not sure, but, you know, that's a reasonable inference that they need to have some other step in there if they don't have a method of amplification. Depends on what they're looking for, and I don't know what products they're trying to develop, but it makes sense to me that that's why they probably --

MR. LIPSEY: I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 212 a November 1, 2001 e-mail from Stephen Swinton to Kary and Nancy, who I presume are Kary and Nancy Mullis.

(Defendant's Exhibit 212 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Okay. What is Exhibit 212?

A It's just like you described it, it looks like an e-mail from Steve to me and Nancy.

Q Okay. And --

13:44 A And then I've written some stuff on the bottom of it there just because it was laying on the desk top.

Q Okay. And this e-mail was yesterday, right?

A Yes, I think it was.

Q Okay. And you've been talking to Mr. Swinton yesterday and today, right?

A Right but this -- I say this little piece of paper, it wasn't like addressed to him necessarily. It was just on the table in front of me.

Q But it was on the table in front of you during your conversations with Mr. Swinton, right?

A No. I think I wrote this just before the game 13:45 started last night, something like that, and it was just sitting there, and I had a pencil in my hand, and I wrote that on it.

Q The handwriting is yours?

A That's mine.

Q Would you read into the record what you've

written in the box there at the bottom.

A "TMA is not quite as specific as PCR thus the need for prepurification. But if non-specific amplification is not that different from specific amplification, what is all of the excitement about. (As in the Nobel Prize)" that sort of thing.

13:45 I mean, somebody knows, besides me and you out there, that specific amplification is the ticket, right? It's the thing that transformed molecular biology. It is not, you know, the non-specific amplification methods that were proposed prior to PCR of being able to do something like that. Those didn't work.

There is a big difference. Regardless of what you may think about it, there is a big difference in a practical sense. You can't do all of the tricky things

13:46 you can do with PCR with non-specific -- non-specific amplifications, even if you use target capture methods. It's been shown by experiment.

Those people that wrote these patents didn't make any products that made any money. It's ridiculous that you're trying to say well, because of that this is a great invention, and it also includes everything else that has been done in DNA chemistry since this. It's like, what an incredibly horrible thing to have to defend. I feel sorry for you.

Q Well, we'll see in the end, Dr. Mullis. You should feel sorry for one of us, I will go that far.

But referring back to what you read -- I'm afraid your answer is a little incomplete. The part that is in your handwriting on Exhibit 212 that is in the box that you've drawn at the bottom says "TMA is not quite as specific as PCR thus the need for prepurification," did I read that correctly?

A That is my speculation, because I really wasn't there when they were designing that system, but that made sense to me. I said, this is probably why they wanted a prepurification of some sort, a sequence directed prepurification, you know, and I put the box around there later. I wrote it all as one paragraph, so that's why I decided to read it. I don't like taking things out of context.

Q Just by prepurification, you're referring to the target capture step, right?

A Yes, something like that.

Q And the box you drew is around that first sentence?

A The box I drew is certainly around it, but I also had written the other stuff underneath it.

Q Would you turn to page 13, please. The second complete paragraph there, the second sentence says, "For

example, Gen-Probe's amplification method generally uses two primers." Do you see that?

13:48 A Yes.

Q Okay. My question is the same as the one I asked earlier, which is, under what circumstances would Gen-Probe's method use something other than two primers?

A You know, I think I've been a little liberal with the word generally. I think my familiarity with their method is it always uses two primers.

Q Would you turn to page 14, please. You may
13:49 wish to read the paragraph surrounding this to get the context to answer my question.

In the middle of that first paragraph on page 14 you make the statement, "The T7 RNA Polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence." Do you see that?

A Yes.

Q Now, in point of fact, in the Gen-Probe
13:49 assays, the target sequence has been separated from the other nucleic acids in the sample prior to association of the T7 promoter sequence with it; isn't that right?

A Well, I'm not sure exactly how they do it, I'll trust you on that one, but you can start this sort of procedure, which I, by the way, invented a long time

ago, this same thing that they call TMA right now, and you can start that with a nucleic acid that hasn't been prepurified, and the promoter sequence attaches itself specifically by sequence to the target sequence. Because one end of that primer is the promoter sequence which is general for T7, and the other part of it is the specific sequence that brings that in to the sequence you want to amplify.

Q But as far as you know in the TMA -- in the process used in the Gen-Probe assays, the T7 promoter sequence is not associated with the target sequence until after it's been separated from the sample; is that right?

A I -- I'm just saying I haven't looked at the instructions on their kit, but that makes sense if they want to prepurify it and then do the TMA procedure, that's what would happen.

Q Okay. In your opinion, had there been in December of 1987 a technique for detecting a nucleic acid in a sample that employed specific amplification as by PCR, would it have been obvious to substitute in that technique non-specific amplification?

MR. SWINTON: Beyond the scope of his opinion, incomplete hypothetical, calls for a legal conclusion, vague as to "obvious."

BY MR. LIPSEY:

Q But other than that, a fine question.

A It might have been obvious to you. It wouldn't have been obvious to me. You know, I knew the ropes there and I said no, why would you? I mean, what would you hope to accomplish by that? It's the same -- it's a different thing altogether, isn't it?

13:52 Q I'd like the reporter to mark for
13:53 identification as Defendant's Deposition Exhibit 213 a January 23, 2001 draft that appears to have been
13:53 prepared by Dr. Mullis, but we will find out.

(Defendant's Exhibit 213 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q First of all, have you seen Defendant's Deposition Exhibit 213 before?

A Me? Have I seen this?

13:54 Q Yes.

A Yes.

Q What is it?

A It's like a note that I probably sent to Bill while we were, you know, discussing all of these issues and I was reading the patents and stuff like that.

Q By Bill, you mean Bill Bowen, counsel for Gen-Probe?

A Yes, Bill Bowen.

Q This bears the date January 23, 2001. Is it your belief that is about the time it was prepared?

A Yes, I imagine it was.

Q And the first paragraph starts off by talking about the invention described in the `338 patent; do you see that?

13:54

A Yes.

Q Is it your belief that you had the `338 patent at that time?

A Yes.

Q Now, in bold in the center of the first page, you've got an entry with the heading "But Look At This" with multiple exclamation marks; do you see that?

13:55

A Yeah.

Q In bold you describe a -- well, you state "People were and still are snatching mRNAs out of extracts with oligo-dT-cellulose every day, eluting them, and then doing RT-PCR on them." Do you see where I've read?

A Yes.

Q Okay. Now, what does RT-PCR mean in that context?

13:55

A It means when you want to start a PCR reaction from an RNA instead of from a DNA, you do reverse

transcriptase first. It's like a --

Q Okay, but RT-PCR as used there is a specific exponential amplification technique?

A Yeah, it's a PCR reaction where the first step is to convert an RNA to a DNA, and after that it's the same thing as just a normal PCR.

Q Then two sentences after that, you state, "I think this fairly common process reads directly on Claim 1, A, B and C," double exclamation mark. Do you see where I've read?

A Yes. I'm referring to the fact that I don't think -- it looks to me like what is actually -- why was this patent issued is kind of what I was suggesting. It seems like people were already doing something similar enough that it fell within those claims, and therefore those claims probably shouldn't have been allowed.

Q And your reference there to Claim 1 A, B and C is to Claim 1 of the `338 patent?

A Of the `338, yeah.

Q That's Plaintiff's Exhibit 5, right?

A Of which?

Q I think it's right over there.

A Okay. That would have been what I was talking about.

Q The A, B and C are reference to the

subparagraph in Claim 1; is that right?

3:57 A Excuse me?

Q The A, B and C in Defendant's Exhibit 213 are references to the subparagraphs A, B and C in Claim 1?

A Yeah, that's the whole claim, Claim 1 A, B, C.

Q And subparagraph C in the claim calls for the step of amplifying the target polynucleotide; is that right?

A Um-hum.

Q Okay. And then you go on to say -- having said

13:57 that you think this fairly common process reads directly on Claim 1 A, B and C you then say, "also Claims 2-5, 7-11 and all their derivatives," do you see that?

A Yeah, I'm saying 2 through 5 and 7 through whatever, right, I see that.

Q But that's intended to be a reference to 2 through 5 and 7 to 11?

A 2 through 5, 7 through 11.

Q Of the `338 patent?

13:58 A And the various ones that are derivative on those claims, I guess.

Q But of the `338 patent?

A Yes.

Q I'd like the reporter to mark for identification --

MR. SWINTON: Before you get to the next one, I have to take a personal break for about two minutes so let's go off the record.

THE VIDEOGRAPHER: This is the end of tape number 2 of Volume 1. We're off the record at 1:58.

13:59 (Recess.)

14:02 THE VIDEOGRAPHER: This is the beginning of

14:02 tape number 3, Volume 1. We're on the record at 2:02.

MR. LIPSEY: I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 214 what appears to be an e-mail from Bill Bowen to Dr. Mullis dated March 27, 2001.

14:03 (Defendant's Exhibit 214 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Have you seen Exhibit 214 before?

A Yes, I have.

Q What is it?

A Well, it's exactly what you said, it's an e-mail from Bill Bowen to me.

Q Is it your belief it was sent to you on or about March 27, 2001?

A Yes.

Q Okay. So that would have been after your e-mail which we marked as Exhibit 213, right?

A Right.

Q Okay. Now, in the last paragraph on the first page, Mr. Bowen states "In order to support our position, we'll need a declaration from an expert witness that if one of skill in the art read the `338 patent, he would understand the inventors to teach a method of amplification using non-specific primers." Do you see where I've read?

A Wait a minute, where is that on this page? Okay. Okay.

Q Did you discuss with Mr. Bowen the possibility of preparing and filing such a declaration?

A Did I discuss with him the possibility of filing such a declaration?

Q Yes, of your filing such a declaration.

A You know, I must have on the phone, I probably said, "Sure, I can do that."

Q Did you, in fact, file such a declaration?

A Well, I -- maybe I didn't actually. I'm not sure if I did.

Q Okay. I mean, such a declaration was prepared, but you did not, in fact, sign and file it; is that right?

A No. I don't think I decided not to. I still agreed with that notion. That's what that -- that's

what all of the examples in the patent described, and the patent was very specific about the fact that, "Hey, we've got this great method where you don't need specific primers. You don't need to synthesize them." So I think if he would have asked me to sign something that says that, I would have gladly signed it.

Have you seen such a thing that I didn't sign? I mean, I didn't read something and say, "No, Bill, I can't sign this." Usually if I didn't like the wording or something, I would come back with my own wording or something. If he asked me specifically to sign something that said that, I would have said sure.

Q Well, let me see if I can refresh your recollection. I'd like the reporter to mark for identification as Defendant's Deposition Exhibit 215 a draft declaration of Dr. Joseph Falkinham prepared in connection with this case.

(Defendant's Exhibit 215 was marked for identification by the court reporter.)

BY MR. LIPSEY:

Q Do you see this draft declaration on the very back page is prepared for signature in April of 2001? Do you see that? It's on the very last page of the exhibit.

A It says --

Q Right at the bottom of the text it says April 2001.

A Mine says "This declaration was executed by me on this blank day of April, Joseph O. Falkinham."

Q Right, so the draft declaration, 215, on its face indicates it was prepared for signature in April 2001, right? That's the date on the back?

A Okay, you're reading that off the front of this?

Q No, I was reading it off the same thing you just read on the last page.

A Maybe I'm going to have to put on my glasses here. I'm not seeing that. What line is that on?

Q The very last line of text before the signature.

A "This declaration was executed by me on this blank date of April 2001, at blank," is that what you want?

Q Right.

A I misunderstood what you were saying.

Q Exhibit 215 appears -- at least on its face appears to have been prepared for signature after the e-mail to you in March of 2001, which we've marked as Exhibit 214, correct?

MR. SWINTON: Objection; lacks foundation.

THE WITNESS: I agree.

BY MR. LIPSEY:

Q And why don't you read the summary of the opinion in paragraph 4 on the second page of Exhibit 215.

A Okay.

14:08 Q Now, the opinion expressed here is "Reading the specification," of the `338 patent, "a person of ordinary skill in the art would not have understood the term `amplifying' as used in the claims of the `338 patent to mean amplifying by use of sequence-specific amplification methods." Do you see that?

A Yes.

Q Were you asked to sign such a declaration?

14:08 A Well, I would have, and I would now, but I don't recall -- I certainly didn't decline to do that. I didn't say, "No, take this to somebody else, I can't do it," because I've certainly expressed that opinion in a couple of other things, I believe.

Q But in the spring of 2001, the March, April, May time frame --

A I would have had the same opinion.

Q -- you did not sign such a declaration, did you?

MR. SWINTON: Asked and answered. We'll

stipulate that. Same answer you gave before when he asked you.

THE WITNESS: I would say I didn't -- as far as I know, I didn't. But I didn't -- Bill didn't send me something and say, "Could you sign this," and I said no and he sent it to Falkinham. That didn't happen, as far as I know. I never saw -- you know, maybe -- I was traveling a whole lot this year, and he may have said, "Well, Falkinham will do it. You don't have to do it." Any idiot could do that actually. It doesn't require a rocket scientist.

MR. SWINTON: On behalf of Dr. Falkinham, I respectfully object, but go ahead.

THE WITNESS: The examples in the patent clearly are non-specific amplification examples. They crow about the fact that you can get away with that and that's what they're inventing, so why wouldn't somebody sign something like that?

BY MR. LIPSEY:

Q Okay. But this particular declaration was, in fact, prepared for your signature?

A It was?

Q Wasn't it?

A I -- frankly, I don't know. I mean, am I supposed to know that?

MR. SWINTON: Argumentative, assumes facts not in evidence.

THE WITNESS: This whole declaration that Randy signed was made for me?

BY MR. LIPSEY:

Q That's what I'm asking.

A Or Joseph -- I don't think so. I certainly did not look this over and say "Get somebody else; I won't do it."

Q Okay. Would you turn to page 8 of the declaration. And specifically to paragraph 33. First sentence there reads in part, "The amplification process described in Example 6 and illustrated in Figure 6 is a cycling method similar to the cycles of synthesis used in the PCR method that I invented." Do you see that?

A Yeah, I see that.

Q Okay, now Dr. Falkinham didn't invent PCR, right?

A Not that I know of. But, you know -- so maybe when he started writing this, he had that in mind, and he just didn't go back and change it when he decided "I'll get Falkinham to do it." But it did not -- there is no -- I didn't refuse to sign this and then he did that. I may have been gone for three weeks or something like that and he got Randy to do it or maybe -- I don't

know, but I mean -- I certainly don't disagree with this thing, and I didn't at the time.

Q I'd like to go back to Defendant's Deposition Exhibit 213. That's your January 23, 2001 e-mail. Do you have that?

14:11

A Okay, got it.

Q And you refer there to the `338 patent and specifically to the combination of target capture with amplification as by Q-Beta-replicase referred to as we

14:12

saw in Example 7 of the `338 patent that is Plaintiff's Exhibit 5, right?

A Yes.

Q And you've stated at the end of that paragraph "Nonetheless, some variant of this method could have obviously been employed prior to a specific nucleic acid amplification such as the polymerase chain reaction." Did I read that correctly?

14:12

A Yes.

Q Now, moving down to the block portion that we talked about before under the heading "But Look At This," you refer there to people snatching mRNAs out of extracts with oligo-dT-cellulose and eluting them.

A Um-hum.

Q Is that a reference to the process of isolating all of the messenger RNA in a sample?

14:13

A Yes.

Q And that process works because all of the messenger RNA has polyA tails on the end of it, right?

A Right.

MR. SWINTON: Beyond of scope of his opinion, incomplete hypothetical.

BY MR. LIPSEY:

Q And by -- the polyA tails will stick to the poly T (phonetic) on the cellulose and thereby separate the messenger RNA from --

14:13 A The rest of the nucleic acid, in particular, the ribosomal RNA, which is the thing you're really trying to get rid of there.

MR. SWINTON: Same objection.

BY MR. LIPSEY:

Q How many different mRNA species are present in a clinical sample?

MR. SWINTON: Incomplete hypothetical.

THE WITNESS: Nobody knows, actually, but we know it's probably less than 260,000, something like that because --

14:14 BY MR. LIPSEY:

Q But it could be as high as 260,000?

A It could be as high as 260. It's generally -- people would -- I think most people would estimate less

in any particular cell type. You know, if you took -- that would be a lot of genes expressing themselves all at the same time.

Q How much less? I mean, what would people say is the number of different mRNA species in a clinical sample?

MR. SWINTON: Beyond of scope of opinion, incomplete hypothetical.

THE WITNESS: If you were to say how many of them are in there at levels of more than, say, 30,000 copies per cell or something that would be a question -- nobody would reasonably ask the question that you asked if they understood --

BY MR. LIPSEY:

Q Let's start with my question, and then we'll answer your question.

How many different mRNA species are there in a clinical sample.

MR. SWINTON: Objection. Beyond the scope, incomplete hypothetical, beyond the scope of his opinion.

I'm sorry, Dr. Mullis, go head.

THE WITNESS: The question kind of doesn't really make sense because they're all in different states of -- there is a whole lot of different ones, we

know that, a whole lot.

BY MR. LIPSEY:

Q Okay.

A For any particular type of one, there is a lot of them that are freshly made with a nice polyA tail. There is a few of them that have just a little less tail and a little less and a little less. There are some of them that are torn up by various things. So they aren't things in the sense of like bbs in a jar, they're all different states of similar stuff.

Then there is high level expression of RNAs and there is low, and there is very low, and there is almost nonexistent. If you try to count all of the different RNA species in a cell, you would be dealing with something that is probably not a rational number. It's probably something that is harder to define than how many. I'm not sure where your question is headed. There is a lot of them.

Q I mean thousands?

A Thousands is probably -- but if you look at the -- like, if you look at experiments that sort of relate to that kind of thing where you just, say, make cDNA clones of every single one of them that you can get through a system, like that poly oligo-dT thing, clone everything, and look at how many different clones you

have, which is not often done, because you have to count them separately, see how many of them are different. There is no probe for one that is there just once, but there are experiments that relate to that, and the answer is probably that at any one time in any one cell line, there is probably 20,000 different species of RNA there in an amount that is significant enough to where you can look at it.

14:16

But I've never seen an experiment that really goes to that exactly. In the experiments that do try, they have -- you know, it's like the things they do at Affymetrix, the things they do at Encyte, where they say what are the levels of like 1400 different ones that we have probes for here, and we put them on this little array and we look at them. That's not really asking the question, how many are there, that's just saying of the ones we have probes for, how many of them are there and in what amount.

14:17

But I would estimate that that would be -- you know, I don't think most of my colleagues would doubt -- they would say, "Yeah, that's probably as good a guess as anybody." What do you need to know for?

Q I was just curious, and I've got you here to ask.

A Well, it would matter what you need to for

know, you say "Because of this" and I say, "Well, this would be a good number for that particular purpose."

Q Okay. Now, this technique that you refer to of snatching all of the mRNA out of an extract using oligo-dT, that technique was used in some of the most famous experiments in molecular biology; isn't that right?

MR. SWINTON: Beyond the scope of his opinion.

THE WITNESS: That's beyond the scope of opinion. But it's been certainly around for a long time, and a lot of people use that. If you want to pull out mRNA.

BY MR. LIPSEY:

Q It was used in the first cloning of a human gene -- or excuse me, the first cloning of a mammalian gene, wasn't it, back in the '70s?

MR. SWINTON: Beyond the scope.

THE WITNESS: I believe you're right, it was used in -- virtually everybody that works with RNA probably has oligo-dT in his pocket somewhere.

BY MR. LIPSEY:

Q Well, in fact, some of the most famous experiments at the very beginning of molecular biology involved isolation of messenger RNA on an oligo-dT column, reverse transcribing it into cDNA and cloning it

in vivo, right?

A Yeah.

MR. SWINTON: Beyond the scope.

THE WITNESS: Therefore, I don't understand why this patent was ever issued, because that does seem to fall under the -- that's what I said to Bill, I said, "How could they possibly have issued this patent?" I mean, generally interpreting those claims would include that. And that was already quite well known in the literature before 1987, so "What is the deal here, Bill?"

14:19

BY MR. LIPSEY:

Q Anybody who had a Ph.D. degree in molecular biology or related science would know about those early experiments; isn't that right?

MR. SWINTON: Beyond the scope of his opinion, incomplete hypothetical, lacks foundation.

THE WITNESS: Apparently Gary Jones didn't have a Ph.D. or didn't know that, huh?

BY MR. LIPSEY:

Q What about Diane Reese?

A Maybe Diane didn't know about that either.

MR. SWINTON: Same objections.

MR. LIPSEY: Can we take a short break.

14:19 THE VIDEOGRAPHER: Off the record at 2:19.

14:20 (Recess.)

1:26 THE VIDEOGRAPHER: On the record at 2:27.

14:27 MR. LIPSEY: Dr. Mullis, Vysis has no further questions for you at this time subject to the requests we've made of your counsel for additional information. Thank you very much for taking the time to come down and talk to us.

MR. SWINTON: I think I have only one question.

14:27 EXAMINATION

BY MR. SWINTON:

Q Dr. Mullis, my question, the only question I have for you really relates in part to some of the commentary of the questions that Mr. Lipsey has asked you, that are at least reflected in part by the questions he asked associated with Exhibit 212. Those were the notes that you placed on a document that happened to be an e-mail that I had sent you the other

14:28 day. Do you remember that?

A Yeah.

Q The only question I have for you is this: Have you had any interaction with anyone at Gen-Probe -- scientists or technical person or lawyer -- by which you learned from them, in fact, why Gen-Probe may use a target capture step in conjunction with TMA?

A No, I haven't actually had -- I mean, that was

just -- I was sort of thinking myself, what would be, why are they do this? I didn't get that from any -- I hadn't ever talked to anybody there, I think, at all.

MR. SWINTON: No further questions.

FURTHER EXAMINATION

BY MR. LIPSEY:

Q Dr. Mullis, just one point. In connection with your activities as a potential expert for Gen-Probe, you have had continuing contact with employees of Gen-Probe and lawyers for Gen-Probe for more than a year; is that right?

MR. SWINTON: Assumes facts not in evidence.

THE WITNESS: The only person I've had contact with that I know is the Gen-Probe employee would be Bill Bowen, who is the lawyer. I haven't been down there to see them. I haven't talked to anybody else. Bill is the only person I've really had contact with at all.

BY MR. LIPSEY:

Q Okay. But Mr. Bowen is both an employee and a lawyer at Gen-Probe, right?

A Yes, so I've talked to him.

Q And you've had extensive discussions and correspondence with him relating to the issues in this case for more than a year; is that right?

MR. SWINTON: Argumentative as to "extensive."

THE WITNESS: Whatever, I mean, I've talked to him about this for over a year, as I mentioned.

MR. LIPSEY: Okay, we have no further questions. Thank you.

MR. SWINTON: Nothing further.

14:30 THE VIDEOGRAPHER: This is the end of tape No. 3 of Volume 1 and concludes the deposition --

MR. SWINTON: Why don't we take the video record off and save a little bit of -- and we'll -- we'll memorialize the stipulation that we ought to be able to use for all of our experts, I assume.

I propose, Charlie, that for all of the experts we use the same scenario we did, I think, for the fact witnesses.

If you will provide the original deposition to 14:30 me, I'll ensure that Dr. Mullis signs it, reviews it, signs it under penalty of perjury and we'll provide you with any corrections that may be made to that.

MR. LIPSEY: Is there a customary time frame on that just --

MR. SWINTON: Only if -- expedited only if you're paying for it.

MR. LIPSEY: I'm saying in terms of your providing --

MR. SWINTON: What have we been doing, 30 days?

MR. BURWELL: 30 days, is that going to give us enough time?

MR. LIPSEY: Well --

MR. SWINTON: He is not -- I don't know what you're planning to do anyway for a hearing, but I doubt -- I'm not going to be in a position to agree that Dr. Mullis would see something in the next day that you have prepared and sign it. If you need a stipulation, do whatever you intend to do with the draft, I'll reserve my objections, and at least within 30 days after receipt Dr. Mullis will sign it.

MR. LIPSEY: Fair enough.

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I, KARY B. MULLIS, Ph.D., do hereby declare under penalty of perjury that I have read the foregoing transcript; that I have made such corrections as noted herein, in ink, initialed by me, or attached hereto; that my testimony as contained herein, as corrected, is true and correct.

EXECUTED this _____ day of _____, 2001, at _____, _____.
(City) (State)

_____

KARY B. MULLIS, Ph.D.

I, the undersigned, a Certified Shorthand Reporter of the State of California, do hereby certify:

That the foregoing proceedings were taken before me at the time and place herein set forth; that any witnesses in the foregoing proceedings, prior to testifying, were placed under oath; that a verbatim record of the proceedings was made by me using machine shorthand which was thereafter transcribed under my direction; further, that the foregoing is an accurate transcription thereof.

I further certify that I am neither financially interested in the action nor a relative or employee of any attorney of any of the parties.

IN WITNESS WHEREOF, I have this date subscribed my name.

Dated: NOV 6 2001

LINDA L. SILVER
CSR No. 9915